Brain

A Journal of Neurology

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DECEMBER, 1939

BRAIN.

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CONGENITAL MYOTONIA IN THE GOAT.

BY G. L. BROWN AND A. M. HARVEY[1]

(From the National Institute for Medical Research, Hampstead, London, N.W.3.)

WE have recently been able to obtain from the United States of America a number of goats suffering from a congenital form of myotonia. A comprehensive account of what is known of their history has already appeared (Kolb, 1938), and we do not propose to discuss it in any further detail. It is sufficient to say that the similarity between this disease in goats and Thomsen's disease in man is very close, the characteristic symptom in both cases being the involuntary persistence of voluntary contraction.

There have been in the past much speculation and some experimental work on the locus of the abnormality in the human disease. The main question has been whether an abnormal discharge of motoneurones is responsible, or whether it is an abnormality of the peripheral structures, i.e. of nerve, of neuro-muscular transmission, or of muscle itself. The problem has been further complicated by the fact that there has been no clear evidence as to the precise nature of the long-lasting developments of tension, which are so characteristic of the disease. Bremer and Mage (1929), for instance, prefer to regard myotonia as a contracture, closely analogous to the " neuro-muscular contracture " which Bremer has observed in amphibian muscle. The only satisfactory criterion for discriminating between contraction and contracture is the existence in the case of a true contraction of oscillatory action potentials in association with the prolonged tension, and here instrumental errors have played some part. Many observers in the past have regarded the myotonic shortening as a contracture on account of the absence of such potential oscillations from string galvanometer records of gross muscle action potentials. Not only is the

[1] Fellow of the Rockefeller Foundation.

string galvanometer insufficiently fast to show certain oscillatory potentials, but, as our present work has shown, even an instrument capable of following the fastest potential variations may not reveal any definite abnormality in the diseased muscle, if the leads from the muscle are too diffuse. For instance, Eichler and Hattingberg (1938) have found the action potential of myotonic muscle to be essentially normal, and our own experiments show that it may appear to be so, when the recording electrodes are applied so as to lead from a large proportion of the muscles fibres. It is only when records taken from belly and tendon of the muscle are supplemented by a study of the activity of relatively few fibres by means of a more localized lead, such as that provided by a concentric needle electrode, that the full electrical picture can be appreciated.

The recent developments in the theory of neuro-muscular transmission have given more than a practical interest to investigations on the muscular disease, and the dramatic effects of eserine and its analogues in the therapy of myasthenia gravis have naturally focused attention on the neuro-muscular transmitting mechanism as a likely site of the abnormality in this condition, and by analogy, in congenital myotonia, which is in so many respects the converse of myasthenia. The fortunate provision of an animal, suffering from a congenital myopathy, has enabled us to apply to the investigation of the condition in question the ordinary methods of myographic and electromyographic examination which have proved of use in physiological and pharmacological studies. We have set out to obtain as clear evidence as possible on the following points:—

(*a*) Is the prolonged tension of a myotonic muscle due to a contracture or to a contraction proper?

(*b*) Is it due to an abnormality of motoneurone discharge?

(*c*) If the abnormality is peripheral, is the neuro-muscular transmitting mechanism involved?

The information we have obtained up to the present points clearly to an abnormality of the muscle fibre itself, without any direct involvement of the neuro-muscular transmission or of the central nervous system.

A preliminary account of this investigation has appeared in the *Journal of Physiology* (Brown and Harvey, 1939).

Methods.

The goats which we have used, normal and myotonic, have weighed between 16 and 72 kg. On account of the necessity of maintaining the breed, our myographic examinations of the myotonic goats have been confined hitherto to two animals, one a female of 21 kg., and the other a male of 23 kg. We have, as far as possible, done control experiments on normal animals of the same weight as these two.

Nembutal (sodium ethyl-l-methyl butyl barbiturate) in 10 per cent. solution has been used as the anæsthetic in all experiments. It was given intraperitoneally in doses from 0·8 to 1·2 c.c. per kg. body-weight, and anæsthesia was maintained by additional injections intravenously of 2·0 to 4·0 c.c. per hour. We used the same anæsthetic for the aseptic section of the sciatic nerve.

For the examination of the effects of substances injected at close range into the arterial system of the muscle, we have used either the gastrocnemius or the tibial group of muscles. The gastrocnemius of the goat does not provide a very satisfactory preparation, since not only is the muscle very bulky, but the dissection involved is prolonged and laborious. When the gastrocnemius was prepared we were able to use a technique in no way different from that used in the same preparation in the cat or dog (*cf.* Brown, Dale and Feldberg, 1936), and the same applies to the preparation of the soleus for simple myographic recording. The tibial group of muscles offers in the goat a better preparation, though not an ideal one, since the volume of the muscles into which the injected fluid passes is large, and the record is taken from more than one muscle.

What we have termed the tibial group consists of the tibialis anterior and the two dorsiflexors of the toes, which are bound together in very intimate relation, especially near their origins from the tibia. The skin was incised and the grouped tendons were tied together at the point of insertion of the tibialis anterior. The muscle group was then freed down to its origin at the head of the tibia, the few vessels running from the muscle belly to the tibial artery being tied. This vessel was now ligated at a point about half-way along the tibia, where it is beginning to emerge from the interosseous membrane, and freed as high as possible, all branches being tied. The vessels actually supplying the tibial group are usually so inaccessible as to be well protected from accidental ligature. The popliteal space was now opened by an incision along the outer side of the femur, care being taken to avoid the peroneal nerve, which should lie just posterior to the line of the incision. The popliteal artery was defined, and drawn into a more accessible position by a loose thread around it, and the posterior tibial artery was tied, together with two small muscular branches. This leaves open the anterior tibial vessel which eventually supplies the tibial group. The thread was left round the popliteal artery, and the wound in the thigh was loosely closed. A clamp was now applied to the tibial artery a short distance above the point at which it was tied, and a needle cannula was inserted centrally into the tibial artery just proximal to the point at which it was tied. Arterial injections were made by attaching a charged syringe to this cannula, closing the popliteal artery by traction on the thread around it, opening the clamp on the tibial artery, and briskly emptying the syringe into the arterial system of the muscle. All solutions were injected in a volume of 2 c.c.

For the myographic recording of the tibial group, of the gastrocnemius and of the soleus, the lower limb was immobilized by inserting drills in the lower and upper ends of the tibia and the upper end of the femur, and clamping them rigidly to uprights bolted to the T slots of a large machined bed-plate. The bed-plate carried at one end a hollow bronze pillar, 7·6 cm. in diameter, on which were mounted on movable bosses one bronze tube to carry the drill in the lower end of the tibia and another reinforced bronze tube to carry the myograph proper. The myograph was a flat steel cantilever, the flexions of which under tension were recorded by a mirror. The connexion between tendon and myograph was through a stout steel hook interrupted by an insulating section of fibre.

In some experiments we used the inferior oblique muscle of the eye for electrical, but not for mechanical recording. The lower eyelid was removed and the bone of the lower margin of the orbit, to the extent of about 1 cm., was excised. The conjunctival sac was then opened at the lower pole of the globe and the orbital tissues dissected, until the tendon of the muscle could be located and tied. The globe was then punctured, freed from any attachment to the inferior oblique muscle, and removed. Careful dissection from the middle of the muscle towards the depths of the orbit exposed the branch of the 3rd cranial nerve supplying the muscle. This was freed at its junction with the ciliary ganglion, tied and cut. With reasonable care, there is no danger of interfering with the blood supply of the muscle. Beyond securing the thread attached to the tendon and supporting the head with sand bags no elaborate fixation was necessary for our immediate purpose.

We have found it desirable to maintain constant the temperature and humidity of the air surrounding the muscles exposed for recording. For this purpose we used a transparent celluloid box, warmed by two 36 watt lamps, covered with wicks dipping into distilled water. The hook attached to the tendon passed through a small hole in the top of the box, and the bottom of the box carried a skirt of rubber-dam with which a reasonably air-tight joint could be made between the lower edge of the box and the thigh muscles, with the necessary stands and clamps. A similar smaller box was used for the eye muscle. With this arrangement, the temperature could be kept at any desired level up to 40° C. and complete saturation with water vapour maintained.

For excitation of the nerves supplying gastrocnemius, soleus or the tibial group, two pairs of electrodes in a common insulating cover were applied to the sciatic nerve in the thigh, in such a way that the nerve could be returned to its natural position, and the muscles and skin sutured over it. The two cathodes of the paired electrodes were 1·8 cm. apart, and were both placed peripherally to, and on the side of the nerve opposite to the anodes. In most experiments the first of a pair of single stimuli, and tetani in all cases, were applied through the centrally placed electrodes, and the second stimulus of a pair or both of the pair following a tetanus, through the peripheral electrodes. In the case of the inferior oblique muscle of the eye, the stimuli were applied through a single pair of electrodes placed on the nerve, 1 cm. away from the muscle.

The stimuli were taken from the secondaries of air-cored transformers actuated by the condenser discharges from gas discharge tube circuits (Schmitt, 1932). They were timed by a Lucas pendulum.

For electrical recording we led from belly-tendon by means of small silver pins, the belly lead being earthed and the tendon lead making connexion with the grid of the first stage of a two-valve condenser coupled amplifier, which fed the output stage either of a Matthews' or of a cathode ray oscillograph. The condensers and leaks were of such size that a rectangular pulse gave a deflexion falling to 1/2 value in 0·5 sec. For recording with concentric needle electrodes we used four stages, coupled with small condensers, feeding either a loud speaker or a Matthews' oscillograph output stage.

Acetylcholine chloride was freshly prepared in saline, acidified to pH 4, and eserine and atropine sulphate and quinine hydrochloride solutions were similarly prepared. Purified curarine chloride (King, 1935) was used for producing neuro-muscular block. It was only used by local arterial injection in doses which, although fully effective in the muscle under investigation, were without any detectable general effects.

In the investigation of the effects of denervation, we divided the sciatic nerve, under full anæsthesia and with aseptic precautions, through a small incision in the lateral side of the thigh.

Results.

General Behaviour of the Myotonic Animal.

Full descriptions of the behaviour of these myotonic goats have already been published (*see* Kolb, 1938), and we have little to add to them. The animals may appear perfectly normal when feeding quietly, but sudden exertion of any kind produces the myotonic seizure. The muscles of the flexors and extensors of the limbs are rigidly contracted and stand out beneath the skin. The limbs are immobilized in extension and the animal may fall. After a few seconds the rigidity passes off, and, after one or two failures, the animal regains its feet and can walk away with little disability beyond a stiffness in the limbs. The effects of rest and of different types of exertion are very striking. A myotonic goat, seen for the first time late in the day, after it has been indulging in continuous mild exercise, appears practically normal. If it is now thrown, and made to lie still for three to five minutes, extreme myotonia develops as soon as it has made the convulsive effort of rising to its feet. Similarly, the stiffness of the legs is always worse when the animals are visited early in the morning.

The effect of sudden exertion is most strikingly shown when the animals attempt to jump. The loose box in which our goats were kept contained a low food trough. Two goats, which showed relatively little myotonia with ordinary tests, regularly attempted to jump into this when approached. They were able to insert their fore-limbs, but the effort of jumping produced a myotonic contraction of the hind-limbs of such severity that they remained immobilized for some minutes.

The pronounced influence of rest and of various types of exertion on the degree of myotonia led us to adopt a method of testing, designed to make the conditions as much under control as possible. The goats were suspended in a metal frame from a horizontal bar, 1·5 m. above the ground, by means of two strips of webbing 20 cm. wide, one passing under the chest immediately posterior to the fore-limbs and the other under the belly just anterior to the hind-limbs. The ends of the strips were attached to the horizontal bar by catches, which could be released suddenly and simultaneously. The goats were lifted into position with as little disturbance as possible, and suspended with their feet just clear of the ground for a given time. During the period of suspension they usually rested quietly without any struggling or attempts to free themselves. When the catches were released, the goats invariably ran forward one or two steps before they were immobilized by the myotonia. The time between dropping and the moment of crossing a low step leading to their dwelling was taken as an index of the degree of myotonia.

Tested in this way, four of the goats have shown remarkable constancy

in their responses over a period of months. Thus, after three minutes suspension, the time in one animal has varied between ten and fifteen seconds, and in a third seven and twelve seconds. An increase in the time of suspension increases the duration of the myotonic rigidity; one animal, which had given figures of eight and six seconds in the two previous tests with three minutes suspension, took fourteen seconds to pass the step after a suspension of five minutes. A fifth goat showed much less myotonia and more variation in the degree. On one occasion she showed no stiffness after three and ten minutes suspension and only six seconds after fifteen minutes. On another day she showed fifteen seconds of stiffness after a rest of only five minutes.

It is perhaps worthy of notice that the change in environment and diet, consequent on the removal of the goats from a Tennessee farm to the Medical Research Council's farm at Mill Hill, does not appear seriously to have altered the myotonia. One of the animals now in our possession was the subject of some studies by Dr. Kolb in 1938, and he informs us that, although it is difficult to make accurate comparisons, there seems to be little alteration in the degree of her myotonia.

These animals show very clearly the local response of the muscle to mechanical stimulation, which is so characteristic of myotonia in man. We clipped the hair over the region of the hamstring muscles, and, with the leg flexed on the belly, struck the skin over the muscle sharply with a percussion hammer. The resisting contraction raised the skin into a roughly spherical swelling some 7 cm. in diameter and 2 cm. in height, which persisted for five to ten seconds. Such a response can be elicited regularly and can be repeated indefinitely, provided a few seconds are allowed to elapse between each blow. We have observed an analogous response also in the fore-limb, tongue and trunk muscles, but it is most easy to elicit in the hind-limb. The contraction resulting from striking is sufficiently strong to cause movements of a limb. If the animal is supine and the hind-limb is flexed at the hip, with the knee and hock at the same level, a blow on the tibialis group of muscles causes a brisk elevation of the foot, which stays raised for some five seconds, and then gradually falls back to its previous position.

These local responses to mechanical stimulation are not obviously diminished by full surgical anæsthesia.

Examination with Needle Electrodes.

The goats were anæsthetized with nembutal and the electrical behaviour of the muscles was examined by inserting concentric needle electrodes.

The immediate effect of inserting an electrode into one of these muscles is very striking, and more particularly so if the amplified action potentials are led into a loud-speaker. The muscle appears to be in a state of incessant activity. Groups of fibres suddenly commence to fire at frequencies

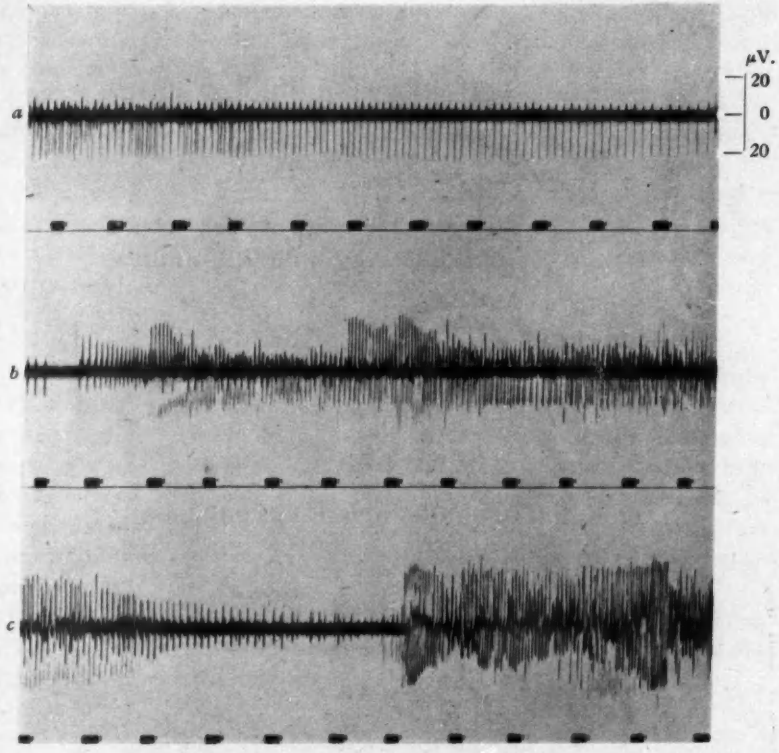

FIG. 1.—Myotonic goat. Action potentials of tibial muscles, concentric needle electrodes. (*a*) Insertion of needle ; (*b*) after movement of needle ; (*c*) after stroking skin. Time 0·2 sec.

varying from 100 to 10 per second. The duration of the discharge in different groups of fibres varies enormously Some may fire at high frequency for only a second or two, others may discharge at a steeply declining frequency for less than a second, while others may fire steadily at a rate of a few per second for some minutes (fig. 1). If the needle electrode, after insertion, is not touched, the discharge dies down, and

there appears to be little, if any, entirely spontaneous activity. The muscle, however, is exquisitely sensitive to mechanical stimuli; even stroking the skin with the finger over or near the recording electrode is sufficient to set up intense activity (fig. 1). As might be expected, tapping or stretching

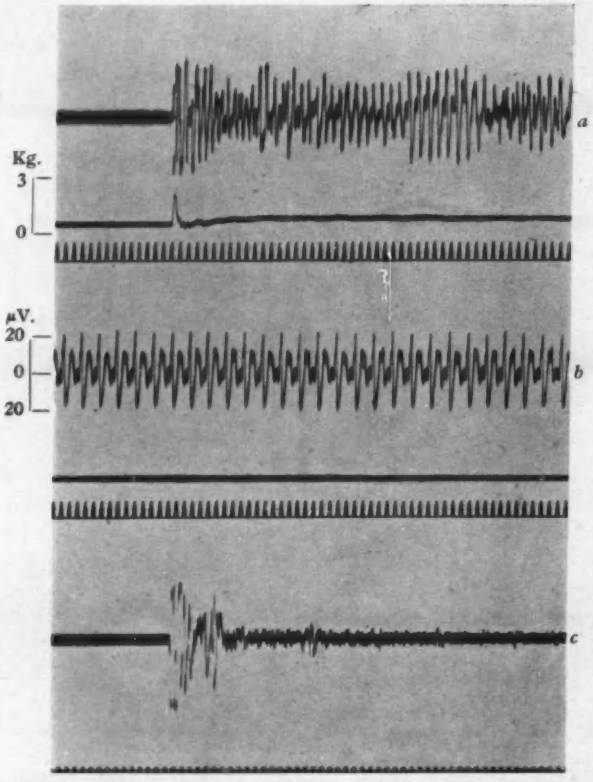

FIG. 2.—Myogram and action potential of tibial group. Effect of tapping tendon. (*a*) Myotonic goat; (*b*) 20 sec. later; (*c*) normal goat. Concentric needle electrodes. Time 10 msec.

the muscle will regularly produce electrical outbursts lasting several seconds.

The recorded potentials from the responses to mechanical stimulation show that there is great variation in the degree of synchronization among the fibres. Some of the persisting discharges resulting from the insertion

of the needle show potentials so constant in size and frequency, and of such magnitude, as to suggest that they are the responses of single muscle fibres. In other cases, the size and constancy of the discharges suggest that the response is due to the synchronized discharge of single motor units. Fig. 2*b* shows a particularly striking example of such a response of constant frequency which is too great to be due to a single fibre and is almost certainly due to the synchronized potential changes in the fibres of at least a motor unit.

We have tested thus with concentric needle electrodes the flexors and extensors of both fore- and hind-limbs, and also the extrinsic ocular muscles and from all of these the abnormal discharges have been recorded.

The response of the muscle of a normal anæsthetized goat to tapping is strikingly different from the myotonic response. The blow is followed by a brief outburst of very asynchronous potentials, which lasts at the most one second (fig. 2*c*).

Effect of Nerve Section.

Isolation of the myotonic muscles from the central nervous system by section of their nerves produces no obvious alteration in their responsiveness to mechanical stimulation. In one animal, we divided the sciatic nerve aseptically in the thigh, and examined the leg muscles with concentric needle electrodes on alternate days for eight days. We could detect no diminution whatsoever in the responsiveness of the muscle to mechanical stimulation; in fact, we received the impression that any change was in the direction of an increase.

It should be noted that in the normal animal, also, decentralization of a muscle or degeneration of its nerve does not diminish the brief discharge which is evoked by tapping.

Myographic Examination.

(*a*) *Response to Single Nerve Volleys.*—The isometric tension maximum attained by the myotonic muscle, in response to a single maximal shock applied to its nerve, is greatly in excess of that of the corresponding muscle of a normal English goat of similar weight. For instance, the twitch-tensions recorded in the tibialis muscles of normal goats, between 16 kg. and 25 kg. body-weight, were from 1·1 kg. to 2·6 kg., whereas the tensions recorded in the myotonic goats were between 3·7 kg. and 4·4 kg. The duration of the twitch, if it is measured from the beginning of tension development to half-relaxation in warm muscles, shows only a slight difference between normal and myotonic muscles, but the time to full

relaxation is longer in the myotonic. Thus, single maximal twitches of normal tibialis muscles had a duration to half relaxation of 120 msec., and to full relaxation of 170 msec.; myotonic tibialis muscles gave figures of 150 msec. and 260 msec. for the same intervals.

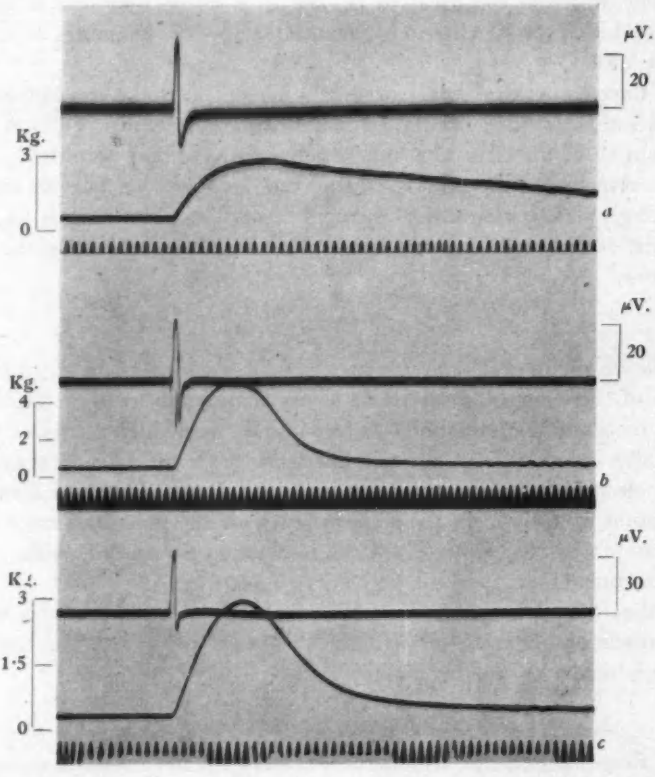

FIG. 3.—Myogram and action potential (belly-tendon) in response to single maximal nerve volley. (*a*) Normal tibial group (muscle cold); (*b*) myotonic tibial group; (*c*) myotonic soleus, another goat. Time 10 msec.

The Action Potential.—The action potential, recorded from belly to tendon, may show relatively little abnormality, or it may be clearly repetitive (fig. 3). Fig. 3*b* was taken from the tibialis group of a goat which showed less myotonia in both physical and myographic examination than the goat from which fig. 3*c* was obtained. The peculiarities of the

myotonic muscle are best revealed by the use of the more localized lead provided by concentric needle electrodes. Fig. 4 shows the prolonged discharge which may follow a single nerve volley. The use of concentric needles also brings out very strikingly the effects of repeated stimulation; the first of a series of responses always shows much more repetitiveness than the last, and, incidentally, the twitch-tension is greater in the earlier responses of a series. Such a decline in twitch-tension during a series is

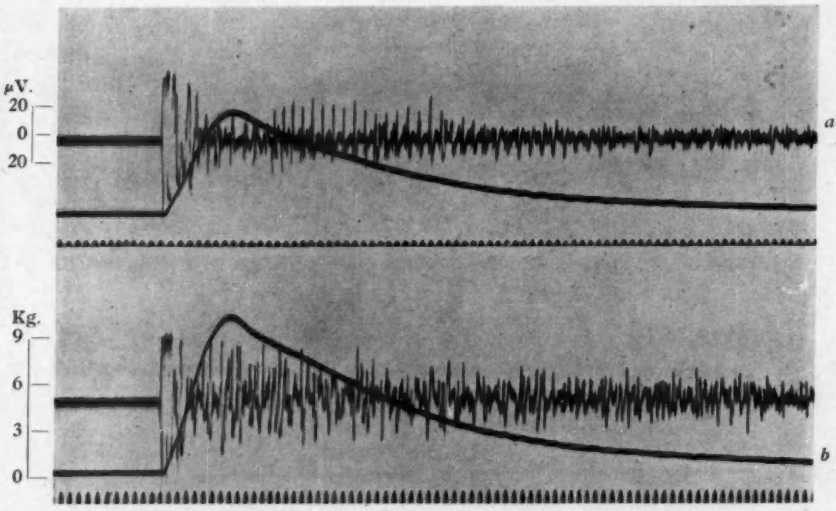

FIG. 4.—Myogram and action potential (concentric needle) of myotonic tibial group in response to (*a*) single maximal nerve volley; (*b*) two volleys 7 msec. apart.

abnormal, since normal muscles always show some degree of "staircase effect."

(*b*) *Response to Double Nerve Volleys.*—We have made some determinations of the least interval at which two nerve volleys produce two responses in the muscle. The most accurate measurements have been made on the electrical responses of the 3rd nerve—inferior oblique muscle preparation, which, as we pointed out above, shows myotonia to a degree little different from the other muscles. In the normal goat, a second electrical response in the muscle appears when the stimuli are applied to the nerve 0·7 to 0·8 msec. apart and the second electrical response is equal to the first when they are 3 msec. apart. In the myotonic goat a second

response appears at the same intervals, and the recovery curve of the second action potential does not differ significantly from the normal. Similar determinations on the soleus muscle and the tibialis group show that in both normal and myotonic muscles of the hind-limb a second response is just detectable when the second stimulus to the nerve follows the first after 1 to 1·5 msec. The muscular summation curve, relating tension maximum to intervals between two nerve volleys, does not differ significantly in the normal and the myotonic muscles.

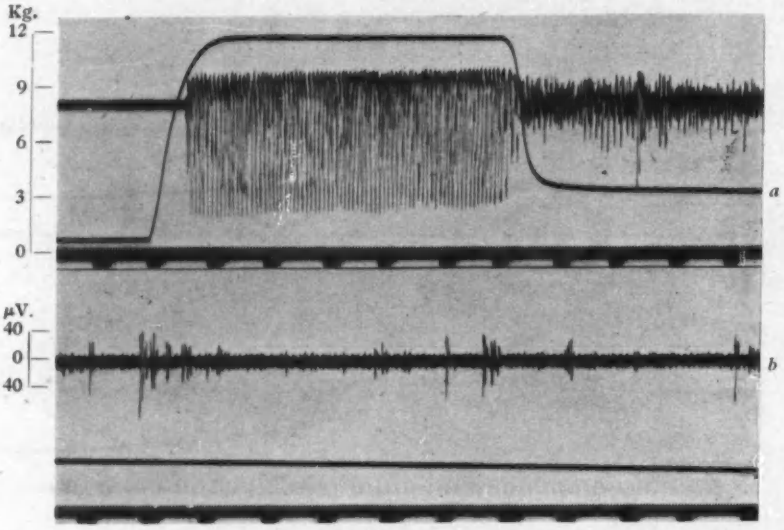

FIG. 5.—Myogram and action potential (concentric needle) of myotonic tibial group. (*a*) Response to maximal stimulation of nerve at 50 per sec.; (*b*) 10 sec. later. Time 10 and 200 msec.

The amount of repetitive discharge in the myotonic muscles is much greater after two nerve volleys than after one, if the interval separating the volleys is less than 10 msec. It is, of course, very difficult to make any quantitative comparison, on account of uncontrolled movements of the needle electrodes and variations due to the amount of previous stimulation but, as shown in fig. 4, the intensity and duration of the repetition after two nerve volleys are much greater than after a single volley.

Effects of Tetanic Stimulation of the Nerve.

The ratio between the single twitch tension and that developed in a fully fused, maximal tetanus is little different in the myotonic goat from

the ratio observed in the normal animal. Figures of 2·5 to 3 are usual in the tibialis group of both types.

The most striking result of a tetanic stimulation of the nerve of a myotonic muscle at frequencies at, or about, the fusion frequency, i.e. 60 to 80 per second, is the prolonged maintenance of tension by the muscle after the stimulation has been interrupted. As shown in fig. 5, a stimulation at 50 per second for 1·2 seconds may be followed by a persisting contraction

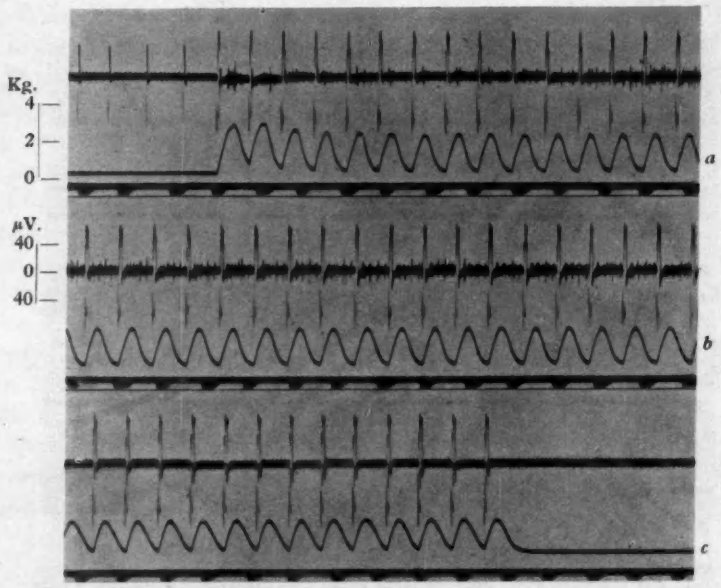

FIG. 6.—Myogram and action potential (concentric needle) of myotonic tibial group. (*a* and *b*) Continuous record of response to nerve stimulation at 7 per sec.; (*c*) 10 sec. after. Time 0·2 sec.

of quite considerable tension. In this particular experiment, the muscle had not completely relaxed to its initial tension some 15 seconds after the end of the stimulation. As is clear from the illustration, this after-contraction is accompanied by oscillatory action potentials in the muscle. The resemblance between this long persisting contraction and the rigidity following a sudden voluntary effort is sufficiently obvious to need no further comment.

The effects of stimulation of the motor nerve at frequencies well below

the tetanic fusion frequency are strikingly different from the effects of higher frequency stimulation. There is usually a slight increase in the degree of repetitive discharge during the first few responses, but, as the excitation is continued, the repetitiveness diminishes, and, at the end of the stimulation, the response may be little different from that of a normal muscle (fig. 6). Again, it is hardly necessary to point out the similarity between this phenomenon and the relief of the myotonic symptoms by the rhythmic activity of mild exercise.

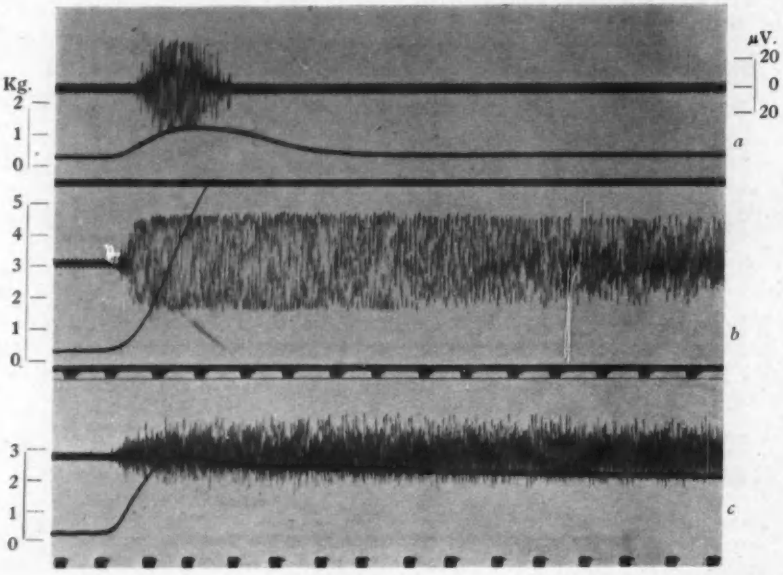

FIG. 7.—Myogram and action potential (concentric needle) of tibial group in response to arterial injections of acetylcholine. (*a*) Normal goat, 100 μg.; (*b*) myotonic goat, 100 μg.; (*c*) myotonic goat, denervated muscle, 2 μg. Time 0·2 sec.

Reactions to Acetylcholine.

As we have already pointed out, the goat does not offer any particularly suitable preparation for the technique of close-arterial injection. The tibialis group is in many respects the most satisfactory, and in normal goats responses equal in tension to the maximal nerve twitch-tension have been obtained with doses of acetylcholine of between 20 and 100 μg., injected into the blood-vessels of the muscles in a volume of 2 c.c. These responses are, as in the cat, brief and twitch-like, and are accompanied by a brief outburst of oscillatory action potentials (fig. 7).

In the myotonic muscle, the dose required to produce a contraction equal in maximum tension to the twitch-tension has varied between 50 μg. and 100 μg. Although approximately the same doses of acetylcholine are required to produce an equivalent tension maximum in the myotonic as in the normal muscle, a given dose of acetylcholine produces in the myotonic a response of very much greater duration. For instance, a myotonic muscle, which had received a dose of acetylcholine sufficient to produce a contraction equal to the maximal twitch-tension, had not fully relaxed 30 seconds after the injection. In a normal muscle a response of similar tension is over in less than one second (fig. 7). This response of the myotonic muscle to acetylcholine is accompanied throughout its long duration by action potentials.

We have investigated the effect of the prolonged contraction resulting from the injection of acetylcholine upon the response of the muscle to simultaneous excitation through its nerve. In one experiment, we stimulated the nerve with single maximal shocks at a frequency of one per second and, without intermitting the stimulation, we injected 100 μg. of acetylcholine in 2 c.c. into the arterial system of the muscle. The contraction in response to the acetylcholine was at least three times the twitch-tension, and lasted some 20 seconds. Measurements of the tension of twitches excited through the nerve during the acetylcholine response, and of their accompanying action potentials, showed that, even when superimposed upon a contraction of magnitude equal to the normal twitch-tension, the nerve twitch still attained 71 per cent. of its original strength, and that the action potentials were never reduced by more than 20 per cent.

Reactions to KCl.

Normal goat muscle is not particularly easy to excite by injected KCl. In one animal, a dose of 100 mg., injected arterially into the tibialis group in a volume of 2 c.c., produced a contraction, with a tension maximum only one-third that of the twitch-tension, and in another, a large goat of 72 kg. body-weight, 200 mg. produced only a just visible contraction. No dose of less than 40 mg. has evoked a perceptible response in this muscle group in any of our normal goats.

In the myotonic goat, on the other hand, 10 mg. in 2 c.c. produced a definite mechanical response, and 20 mg. caused a long lasting contraction, which reached a tension of 4·62 kg., or nearly double the nerve twitch-tension (fig. 8). In this particular instance, the contraction lasted more than three minutes, and throughout its course was accompanied by a violent, unbroken oscillatory electrical discharge (fig. 8). So sensitive,

indeed, is the myotonic muscle to KCl that we have observed electrical outbursts resulting from injections of 4 mg. in 2 c.c., or only five times the normal concentration of KCl in Locke's solution. These responses seemed clearly to be the consequence of the raised K^+ concentration, since similar injections of isotonic NaCl solution were without effect.

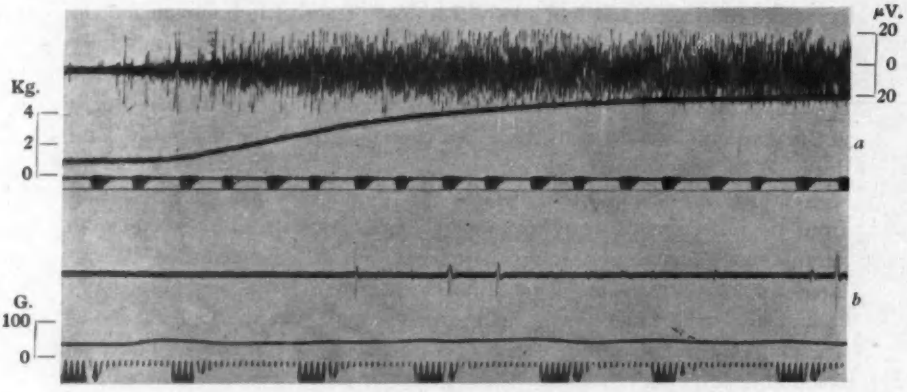

FIG. 8.—Myogram and action potential (concentric needle) of tibial group in response to arterial injection of KCl. (*a*) Myotonic goat, 20 mg.; (*b*) normal goat, 100 mg. Time 10 and 200 msec.

Effects of Curarine.

In the expectation that curarine would modify profoundly the myotonic phenomenon, we gave the drug by close-arterial injection in small, increasing doses. We found, however, that curarization of the muscle did not, at any stage, modify the characteristic responses of the myotonic muscle to mechanical stimulation. Thus, in one experiment, a dose of curarine, which had reduced the nerve twitch-tension to one-tenth of its original value, in no way altered the response of the muscle to tapping; and this latter response persisted unchanged when the muscle would no longer respond to nerve stimulation.

As might be expected from previous work (Brown, 1937*b*), full curarization is similarly without effect on the response of these muscles to KCl.

We have as yet insufficient data to justify any full account of the effects of curarine on the responses to injected acetylcholine. In normal muscle, acetylcholine ceases to be effective at a stage of curarization at which the motor-nerve twitch-tension is not yet greatly reduced. In the one experi-

ment which we have made on the myotonic goat, the response to 100 μg. acetylcholine was reduced to one-seventh of its previous value by a dose of curarine which had just eliminated a visible tension response to nerve stimulation.

Effects of Denervation.

As we have stated above, division and degeneration of the nerve supply of the myotonic muscle has no immediate effect upon its abnormal sensitivity to mechanical stimulation.

Denervation, as in normal muscle, increases the sensitivity of myotonic muscle to injected acetylcholine. An injection of 2 μg. of acetylcholine produced a contraction attaining a maximum tension of 2·2 kg., which was of such duration that it had not quite attained one-half relaxation in 20 seconds (fig. 7). An injection of 10 μg. produced a response of 4·3 kg. and of similar duration. Both these responses were accompanied throughout their course by oscillatory action potentials, and, in fact, we have not observed, with doses of acetylcholine up to 10 μg., any sign of the characteristic "silent period" which accompanies the responses to acetylcholine of large tension in the denervated muscle of a normal animal. Denervated myotonic muscle responds readily to KCl injections, and probably shows some degree of sensitization as compared with the innervated myotonic muscle. A very prolonged response, accompanied throughout by oscillatory potentials, and attaining 2·1 kg. tension was obtained with 10 mg. of KCl, injected arterially into the tibial group of a myotonic goat.

Effect of Other Alkaloids.

The known curative effect of quinine on myotonia, both in man (Wolf, 1936) and in the goat (Kolb, 1938), led us to examine the effects of this substance on the abnormal sensitivity to mechanical stimulation. Fig. 9 illustrates its actions, and is of additional interest in that the responses were recorded from a muscle which had been denervated for eight days, and had already received a full dose of curarine. In A is shown the effect of a tap applied to the belly of the muscle. Between A and B the muscle received 3·5 mg. of quinine by arterial injection. In B the muscle was again tapped, and gave a response little greater than that occurring in normal muscle.

Eserine, in a dose of 200 μg., injected arterially into the tibialis group of a normal goat, produces at least a 50 per cent. potentiation of the nerve twitch-tension. Into the corresponding muscle group of a myotonic goat we injected doses of 20 to 40 μg. of eserine without producing a

recognizable modification of the nerve twitch. In a subsequent experiment, the injection of 200 μg. into the tibialis group of a myotonic goat produced a potentiation of twitch-tension little different in extent and duration from that observed in the normal animal. On this evidence we can only conclude that the myotonic muscle is not greatly, if at all, more sensitive to the action of eserine than is the normal muscle.

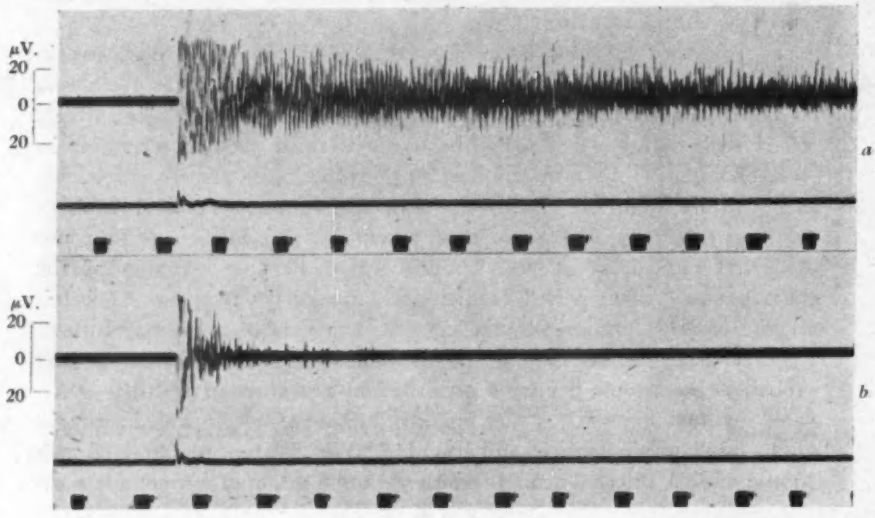

FIG. 9.—Myogram and action potential (concentric needle) of denervated and curarized myotonic tibial group in response to tapping. (*a*) Before and (*b*) after arterial injection of 3·5 mg. quinine. Time 0·2 sec.

DISCUSSION.

Most authors who have investigated goats suffering from this congenital abnormality have been in little doubt that the condition is so like Thomsen's disease in man as to be indistinguishable from it. With this view we fully concur. Apart from the stiffness which accompanies any sudden muscular activity, one of the most striking abnormalities to be seen, both in man and in the goat, is the local contraction of the muscles which results from a sharp blow upon them. It has been customary to refer to this as a "contracture," but our results make it quite clear that this description is incorrectly applied. A contracture in a muscle is an unpropagated, localized response, and, as such, has no accompanying action potential of the rapid type normally associated with propagated contraction.

Slow potential changes between the active and passive portions of a muscle in contraction may admittedly exist; but the true, rapid oscillatory wave accompanying a propagated contraction is characteristically absent (*cf.* Gasser, 1930; Brown, 1937 *a*). We have shown, we think beyond question, that every response of the myotonic muscle, whether to nerve stimulation, to mechanical stimulation, or to an injected chemical excitant, is accompanied by oscillatory action potentials. These responses must therefore be regarded as asynchronous, tetanic contractions of the muscle fibres, and not as contractures. The existence of these oscillatory potentials, as usually recorded by concentric needle electrodes, shows that some part at least of the muscle is in tetanic contraction, though it does not entirely exclude the possibility that a contracture may be involving some of the constituent fibres of the muscle other than those in immediate proximity to the electrodes. Another test, however, may be applied. The state of contracture in a muscle fibre prevents the propagation along it of excitation waves arising from the region of the motor end-plate (Brown, 1937 *a*). There is accordingly a great depression in the responsiveness of a muscle in contracture to stimuli applied to its nerve. We have shown, indeed, that there is some reduction, both in tension and in the action potential of the twitches superimposed on the prolonged response of a myotonic muscle to acetylcholine. This reduction, however, is certainly not too great to be explained by the fact that at any one moment many of the fibres are refractory, as a result of their continued tetanic response to acetylcholine. We are convinced, therefore, that the long-lasting developments of tension in myotonic muscles are due to normally propagated excitations in the fibres, and not to anything of the nature of unpropagated contracture.

Our experiments have given, we believe, an equally conclusive answer to the question of the involvement of the central nervous system in the pathogenesis of the disease. The characteristic responses to mechanical stimulation occur, without perceptible change, in the myotonic muscle, not only after full curarization, but after the nerve endings have degenerated as a result of section of the nerve to the muscle. It would obviously be difficult entirely to exclude the possibility that some abnormality of central discharge might be present, in addition to the demonstrable abnormality of the responding muscle; the symptoms of the disease, however, can be entirely explained by the observed abnormalities of the muscle. As we have pointed out, one of the most striking features of the disease is due to the fact that the symptoms are intensified, or, indeed, may only become apparent, after a sudden muscular exertion. This might be thought to point to a central origin of the disease; but an after-contraction of long

duration follows artificial tetanic stimulation of the cut nerve at suitable frequencies, and it is probable that a sudden sufficiently intense motoneurone discharge would have the same effect, given the same muscular abnormality. Such a motoneurone discharge of the range of frequency found to be most suitable for producing the after-contraction is, in fact, the normal cause of any sudden, vigorous muscular movement. The intensification of the myotonic state by tetanic stimulation or by sudden voluntary exertion, is readily explicable in terms of phenomena observed in the mammalian nerve-muscle preparations. Tetanic stimulation of the motor nerve of a muscle produces an increase in the tension of subsequent twitches, and a long-lasting increase in the excitability of the motor end plates. It has been shown that both these after-effects of a tetanus are probably due to K ions mobilized by the intense activity of the muscle (Brown and Euler, 1938). We have shown that the myotonic muscle is abnormally sensitive to K^+ and this would render it more susceptible than the normal to the after-effects of tetanization.

The effects of mild continuous exercise and, experimentally, of tetanic stimulation at frequencies well below the fusion rate, in relieving the myotonia, are again compatible with known properties of mammalian muscle. Low frequency stimulation, unlike high frequency, can be shown to depress still further the responses of a preparation in which neuromuscular transmission has been partially blocked by curarine (Brown, 1938).

It appears, then, that the myotonia is due to an abnormality of some part of the muscle fibre itself, since the abnormal response of the muscle to direct excitation is essentially unaltered by severance of the nerve, by blocking neuro-muscular transmission with curarine, and even by degeneration of the motor nerve endings. The essential abnormality appears to be a tendency of the muscle fibres to respond repetitively to any form of stimulation. There are certain features of this repetitive discharge which make it remarkable. There is little synchronization among the fibres of the muscle as a whole, judging from the electrical records taken with belly-tendon leads. Examination of fig. 3 shows that, even with this lead, there may be a second distinct spike after the first synchronous response to a single nerve volley, but, as often as not, the repetitiveness is shown by little more than an irregularity in the descending limb and diphasic artefact of the response. The synchronization is, in fact, very much less than is observed in the repetitive discharge which follows single nerve volleys in normal muscle after the administration of eserine in suitable doses (*cf.* Brown, Dale and Feldberg, 1936). The frequency of the discharge, then,

would seem to vary from group to group of muscle fibres, after a single stimulus has been applied. There seems, however, to be some mechanism which gives rise to a local synchronization, since the regular and very long lasting discharges which follow insertion of needles, or, in some cases, tapping the muscle, seem too large to be confined to single muscle fibres, and suggest that the fibres of a motor unit are contracting in very perfect unison. We are unable at present to commit ourselves to any explanation of this synchronization.

In many respects, there is a very close similarity between a muscle in myotonia and one poisoned with veratrine (*cf.* Eichler, 1938; Kolb, Harvey and Whitehill, 1938). Both show prolonged and very asynchronous repetitive responses to single nerve volleys, and in both the abnormalities persist after denervation and full curarization (Bacq and Brown, 1937). Some preliminary experiments which we have made show that a veratrinized muscle exhibits a sensitivity to mechanical stimulation very like that of the myotonic muscle. There is one further point in which the effects of veratrine are particularly suggestive. Bacq (1939) has recently shown that veratrine has a very remarkable effect on frogs' muscle, in sensitizing it to the effects of K ions, and the myotonic muscle is notably sensitive to the same ions. K ions alone, in quite low concentrations, can stimulate many excitable structures, and in sub-liminal concentrations increase the excitability of tissues to other stimuli. Excitation of a muscle certainly causes a mobilization of K ions and even actual loss of K^+, and there is reason to suppose that the myotonic muscle may lose K^+ in excess (Cumings, 1939).

Some mention may be made here of the therapeutic effects of various substances in man and their actions in the goats. Myotonia in both man and goat is relieved by quinine and certain quinine derivatives (*cf.* Kolb, 1938), and we have shown here that the typical response to tapping is absent after the administration of quinine. In the course of a study of the actions of quinine, Harvey (1939, *a* and *b*) found that two of many were likely to be responsible for its curative effects in myotonia, one being its curare-like effect and the other its ability to suppress repetitive responses of all types. Our present work shows that it is probably the latter which is mainly responsible. Any curarizing substance would probably relieve the myotonic symptoms in some degree, simply by diminishing the amount of excitation reaching the muscle; but, as we have shown, no amount of curarine will abolish the abnormal response of the muscle to mechanical stimulation.

Eserine and its analogues, which have such dramatic effects on normal

muscle, might be expected to accentuate the symptoms of myotonia, as clinical experience in man has shown them to do (Russell and Stedman, 1936). This action, however, should not be taken as indicative that an abnormality of the neuromuscular transmitting apparatus necessarily contributes to the peculiar behaviour of the myotonic muscle. In normal muscle eserine changes the response to a single nerve volley from a single contraction into a brief tetanus, and there is no reason to suppose, therefore, that it should do other than accentuate the existing repetitiveness of the response of the myotonic muscle. In any case, an action of eserine in any particular condition should be interpreted with caution since, in addition to its specific effect in protecting choline esters from enzymatic hydrolysis, it can change the direct electrical excitability of the muscle fibre.

SUMMARY.

(1) We have examined myographically and electrically the muscles of goats suffering from a congenital myotonia indistinguishable from Thomsen's disease in man.

(2) The muscles are extremely sensitive to mechanical stimulation; tapping, stretching and the insertion of electrodes cause contraction of the muscle.

(3) This contraction is due to a long-lasting irregular tetanus in groups of muscle fibres, best shown by means of concentric needle electrodes. It persists unchanged after section and degeneration of the nerve and after full curarization of the muscle, but is abolished by a suitable dose of quinine.

(4) The response of the muscle to a single nerve volley is repetitive, and the twitch-tension is greater than in a normal goat.

(5) Tetanic stimulation of the motor nerve at frequencies of the order of fifty per second aggravates the myotonia, and the muscle remains tetanically contracted after the stimulation has stopped. Stimulation at five per second, on the other hand, produces a progressive diminution of the abnormal activity.

(6) The myotonic muscles are not abnormally sensitive to acetylcholine, in that the amount required to produce a given tension maximum is approximately the same as in normal muscle. The duration of the response to a given dose is, however, greatly prolonged in the myotonic.

(7) The myotonic muscles are abnormally sensitive to potassium ions. A dose of KCl which has no effect in normal muscle produces a contraction of considerable tension, lasting some minutes in the myotonic muscle.

(8) Myotonia appears to be due to an abnormality of the muscle fibre

itself, and the neuromuscular transmitting apparatus is not directly involved.

We wish to express our gratitude to the Rockefeller Foundation and to Mr. J. J. Murray. Dr. James Ward, Professor Sam Clark and Dr. O. R. Langworthy for the assistance they gave us in obtaining and transporting the goats.

REFERENCES.

BACQ, Z. M. (1939), *C. R. Soc. Biol.*, **130**, 1369.
——and BROWN, G. L. (1937), *J. Physiol.*, **89**, 45.
BREMER, F., and MAGE, G. (1929), *C. R. Soc. Biol.*, **102**, 336.
BROWN, G. L. (1937, *a*), *J. Physiol.*, **89**, 438.
——(1937, *b*), *Ibid.*, **91**, 4P.
——(1938), *Ibid.*, **92**, 23P.
——DALE, H. H., and FELDBERG, W. (1936), *Ibid.*, **87**, 394.
——and HARVEY, A. M. (1939), *Ibid.*, **96**, 11P.
——and VON EULER, U. S. (1938), *Ibid.*, **93**, 39.
CUMINGS, J. N. (1939), *Ibid.*, **96**, 12P.
EICHLER, W. (1938), *Z. Biol.*, **99**, 243.
——and VON HATTINGBERG, I. (1938), *Dtsch. Z. f. Nervenheilk.*, **147**, 36.
GASSER, H. S. (1930), *Physiol. Rev.*, **10**, 35.
HARVEY, A. M. (1939, *a*), *J. Physiol.*, **95**, 45.
——(1939, *b*), *J. Amer. Med. Assoc.*, **112**, 1562.
KING, H. (1935), *Nature*, **135**, 469.
KOLB, L. C. (1938), *Bull. Johns Hop. Hosp.*, **63**, 221.
——HARVEY, A. M., and WHITEHILL, R. (1938), *Ibid.*, **62**, 188.
RUSSELL, W. R., and STEDMAN, E. (1936), *Lancet*, **2**, 742.
SCHMITT, O. H. and SCHMITT, F. O. (1932), *Science*, **76**, 328.
WOLF, A. (1936), *Arch. Neur. Psych.*, **36**, 382.

OBSERVATIONS ON THE EFFECTS OF TRIGEMINAL DENERVATION.

BY G. F. ROWBOTHAM

(From the Neuro-surgical Clinic of the Manchester Royal Infirmary. This work was carried out under a Research Fellowship in the Neuro-surgical Service of the Manchester Royal Infirmary.)

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I.—INTRODUCTION.

THE following study has been made in order to discover the physiological effects of trigeminal denervation; it is not devoted to the charting of areas of resulting anæsthesia, nor is it concerned with the more therapeutic side of the results though it is interesting to note that in 95 per cent. of the cases a complete relief from pain has been obtained.

Eight hundred people have been treated in this clinic for primary trigeminal neuralgia, root section has been performed on 291 occasions, and there have been two deaths. In the whole series all kinds of operations have been used: avulsion of the supra-orbital, infra-orbital and inferior dental nerves; alcohol injection in the ganglion and into the second and third divisions; intracranial neurectomy of divisions 2, 3 and 1 (in order of frequency); posterior root section in the middle and in the posterior fossæ and division of the trigeminal tract in the medulla oblongata. These experiences have allowed observations on the changes following severance of the trigeminal pathways and particularly on alterations in taste, on the innervation of the cornea, on the proprioceptive pathways of the tongue, on changes relevant to the sympathetic nervous system, and on the ætiology of paralytic keratitis.

MATERIAL.—FIFTY CASES OF TRIGEMINAL DENERVATION.

Root section by the lateral route :—	
Complete	8
Fractional	10
Root section by posterior fossa route	5
Intracranial neurectomy of division 2	4
Intracranial neurectomy of division 1	1
Alcohol injection :—	
Ganglion	10
Divisions	5
Tractotomy	5
Bilateral denervations	2
Total number of cases ...	50

II.—THE SENSE OF TASTE IN THE MOUTH.

In this section an analysis of the changes in taste which accompany trigeminal denervation of the mouth is made and an explanation given to account for their occurrence.

History.—Though the sense of taste has aroused the scientific curiosity of physicians since the days of Æsculapius, it was not until the beginning of the nineteenth century that sustained efforts were made to solve the problems of the anatomy of the gustatory pathways. That these problems have not been finally solved will not cause undue surprise. Any work on the sensory side of the nervous system is beset with particular difficulties since animal experimentation has obvious limitations and quantitative measurements in man are dependent on what must be variable factors, the personal evaluation of a stimulus and the ability to describe the sensation with precision.

Magendie (1822), on dividing the 5th nerve intracranially in dogs discovered that the sense of taste was lost on the anæsthetic side of the tongue. Coming from a scientist of Magendie's reputation this discovery was generally accepted, and obviously influenced the opinion of his successor Claude Bernard.

Bernard, though well aware of the change in taste which accompanies some types of facial paralysis in man, and despite his demonstration of the loss following intracranial division of the facial nerve in dogs, was convinced that taste was conveyed by the trigeminal nerve, and suggested that division of the facial nerve removed a motor phenomenon about the trigeminal nerve endings necessary for the development of an adequate sensory impulse.

However, an alternative theory had already been advanced by Montault (1833) in a thesis entitled " Dissertation sur l'hémiplégie faciale " in which

loss of taste over the anterior two-thirds of the tongue was described in three cases of facial paralysis in man. The accuracy of this important finding has been sustained on many subsequent occasions, but at the time it added obscurity rather than clarity to the gustatory problems.

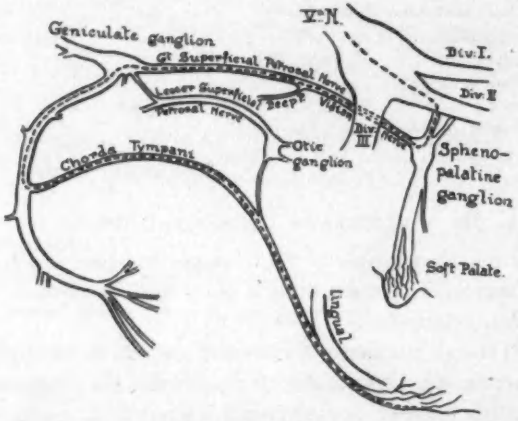

FIG. 1.—The pathway for taste fibres suggested by Schiff.

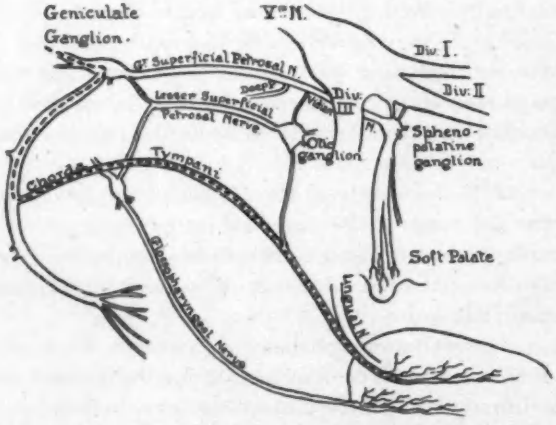

FIG. 2.—The pathway for taste fibres suggested by Lussana.

Thirty-four years later Schiff (fig. 1), as a result of his experiments on animals, believed that taste sensations were conveyed by the chorda tympani to the geniculate ganglion of the facial nerve, then along the great superficial petrosal nerve via Meckel's ganglion to the second division of the trigeminus and so by its posterior root to the brain.

On clinical evidence Lussana (1869) (fig. 2) came to the conclusion that the pathways were not so circuitous; he expounded what has proved to be the modern belief that gustatory fibres are conveyed from the tongue by the chorda tympani nerve to the geniculate ganglion and then pass along the nervus pars intermedius Wrisbergii. This view was not generally accepted and Ziehl (1889) (fig. 3), as Schiff had done earlier, suggested that the trigeminus was the final pathway, the fibres entering the third division after passing through the geniculate and the otic ganglia. Gowers all his life was very strongly convinced that the 5th nerve was the main gustatory pathway from the mouth, and this opinion he declared quite firmly on several occasions. Very strong views were expressed by Dixon, an anato-

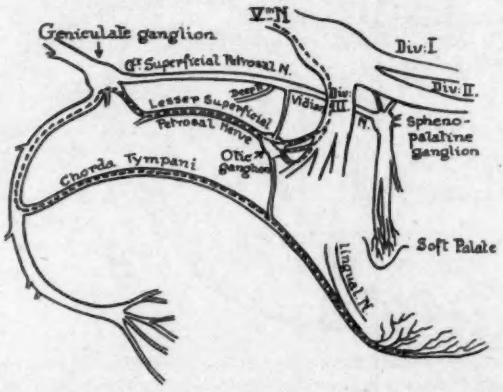

FIG. 3.—The pathway for taste fibres suggested by Ziehl.

mist, against the trigeminal theory, and he argued on embryological grounds against it, pointing out that the nervus pars intermedius Wrisbergii is the post-ganglionic equivalent of the pre-ganglionic chorda tympani nerve, and so must relay gustatory impulses if the chorda tympani is a nerve of taste.

New opportunities for study arose when Hartley (1892) and Krause (1892) succeeded in dividing the trigeminal pathways intracranially in man and again when the manœuvre was modified and perfected by Spiller and Frazier in 1909. Harvey Cushing (1903) reviewed thirteen cases of Gasserian ganglion extirpation and came to the conclusion that the trigeminus does not convey taste to the brain either from the posterior or anterior portion of the tongue. He did admit of a temporary abolition or lessening of acuity of the sense of taste over the anæsthetic part of the

tongue which disappears in a few days; he thought it due to degenerative changes in the lingual nerve compressing or chemically blocking the fibres of the chorda tympani nerve. Dandy (1930), by the division of the 5th, 7th

TABLE I.—LIST OF CASES IN WHICH THE CONDITION OF TASTE WAS OBSERVED AFTER RESECTION OF THE GASSERIAN GANGLION.

(Compiled by Morriston Davies.)

Recorded by	Total	Taste unaffected	Taste impaired	Taste lost
Blüher	1	—	—	1
Cahen	1	—	—	1
Coelho	1	1	—	—
Dandridge	1	—	1	—
Depage	1	—	—	1
Erdmann	1	—	—	1
Eskridge and Rogers...	1	—	—	1
Garre	1	—	1	—
Hutchinson, J., Jun. ...	1	—	—	1
Knock	1	—	1	—
Kruger	1	—	1	—
Marchant et Herbet ...	1	1	—	—
Monari	1	—	—	1
Stewart, R. W. ...	1	—	—	1
Thomas, Lynn ...	1	1	—	—
Weeks	1	—	1	—
Winslow	1	—	—	1
Draudt	2	—	1	1
Friedrick	2	—	1	1
Rose	2	—	1	1
Thomas, H. M. ...	2	1	—	1
Keen	3	—	1	2
Maier	3	—	2	1
Pruschinin	4	—	3	1
Gowers	5	—	—	5
Lexer	6	—	—	6
Tiffany	6	4	—	2
Tiffany	10	4	6	—
Krause	6	1	3	2
Cushing	19	17	1	1
Davies	20	16	3	1
Total ...	107	46	27	34

and 9th peripheral nerves in the posterior fossa separately and in combination, made observations in man of great anatomical precision, and in collaboration with Dean Lewis reviewed his results (1930). They came to the conclusion that section of the 5th nerve does not affect the sense of taste, and that taste sensations travel from the anterior two-thirds of

the tongue by the chorda tympani nerve and are relayed to the brain stem by the nerve of Wrisberg. The posterior third of the tongue is supplied by the glossopharyngeal nerve.

That the glossopharyngeal nerve and the nerve of Wrisberg are the main anatomical pathways of buccal taste there is little doubt, but there is still doubt about the importance of the trigeminal pathways. Wilfrid Harris (1926) was originally very certain that in most cases of trigeminal denervation the sense of taste is lost on the anæsthetic side of the tongue. He said " my clinical experience of 5th nerve paralysis due to disease and when

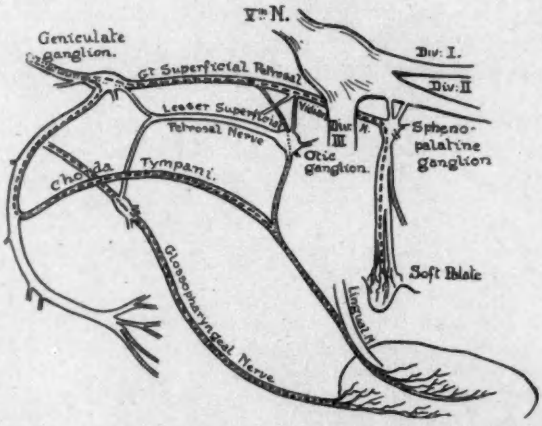

FIG. 4.—The modern conception of the pathways conveying the fibres of taste from the mouth. The finely dotted line denotes an alternative pathway by which the fibres of the chorda tympani nerve enter the geniculate ganglion via the great superficial petrosal nerve instead of coursing along the tympanic part of the facial nerve.

produced by injection of the nerve at the foramen ovale, is, in my opinion, indubitable evidence of the gustatory function of the trigeminus." At first Harris inclined to the view that some taste fibres at least were conveyed by the trigeminal nerve, and in support of this thesis quoted Nageotte's histological research in which fibres leaving the trigeminal nucleus were demonstrated entering the neighbouring gustatory nucleus. As his experience widened he met with conflicting results, in some cases no gustatory changes being observed, and he reviewed his beliefs in less exclusive terms, suggesting that in some way or other there was a correlation and interdependence of function as regards taste in the facial, trigeminal and glossopharyngeal nerves.

Carmichael and Woollard (1933) reviewed 17 cases of alcohol injection into the Gasserian ganglion made by Hinds Howell and they found that taste was lost in 10 of the cases.

Schwartz and Weddell (1938) (fig. 4) came to the conclusion that in some cases impulses subserving taste from the anterior two-thirds of the tongue pass along fibres which leave the chorda tympani to join the great superficial petrosal nerve before entering the geniculate ganglion. This alternative pathway has recently been confirmed by Wakeley and Mulvaney (1939). Damage to the great superficial petrosal nerve in this type of case will produce changes in buccal taste and it has been suggested that it is the variability of this pathway which accounts for the conflicting results found after trigeminal denervation.

This is the point at which the problem rests to-day.

Test 1.—With the tongue protruded a measured quantity of salt was placed on one side of the wet tongue 2 cm. backwards from the tip and 1 cm. medial from the border. With the tongue held gently between the examiner's fingers in the protruded position, the time in seconds was counted until the patient was able to signal his recognition of the taste by raising his hand and then making a statement or by pointing to a chart on which the name of the substance was written. The mouth was then washed until the traces of the salt had disappeared and a similar test carried out on the other side of the tongue. The tests were repeated with cane sugar, vinegar and powdered quinine sulphate.

Results.—Forty cases were tested by this method: twenty cases within fourteen days of the operation and twenty cases from two weeks up to five years after the operation. The average latent period before appreciation on the normally sensitive side of the tongue was thirty seconds.

Cases tested within fourteen days of the operation (usually on the second day):—

Taste was completely lost in	6 cases
Taste was delayed 30 seconds or more in	12 cases
Taste appreciated in the same time as on normal side in ...	2 cases

Cases tested fourteen days or more after the operation (usually several months later):—

Taste was completely lost in	2 cases
Taste was delayed 30 seconds or more in	14 cases
Taste appreciated in the same time as on normal side in ...	4 cases

Precautions were taken to apply the tests under identical conditions as far as was possible. It was found that the pain or discomfort of undue traction or pressure on the tongue by the controlling fingers interfered with the finer appreciations of taste; dryness of the tongue prolonged the normal latent interval and that it was difficult to place the materials on areas which correspond exactly.

Test 2.—The materials were placed on the tongue as in *Test 1*, the patient was then allowed to withdraw his tongue into his mouth, but was asked to keep

the materials confined as far as possible to the experimental areas under test and not to allow them to be freely washed about the mouth with saliva.

The obvious fallacy of the test is that the materials go into solution in the saliva and so diffuse on to areas of the mouth which are not under test at that time. The patients, however, are aware of this, but are able to analyse the sensations coming from the two sides or front and back of the tongue with useful precision, and with results very similar to those just recorded.

Results :—

Taste was completely lost in	2 cases
Taste was delayed 30 seconds or more in	32 cases
Taste appreciated in the same time as on the normal side in ...	6 cases

Test 3.—All the patients were given alternatively salt, sugar, vinegar and quinine asked to take them into the mouth in the ordinary way and to describe in detail the sensations aroused on each side of the tongue and palate.

Results.—Thirty-eight people out of forty were certain that taste for salt, sour, bitter, sweet was impaired on the anæsthetic part of the mouth. Taste was fainter and far less crisp than on the sensitive side and a great effort or concentration was necessary before the substance could be named.

From three patients the following unprompted statements were obtained when it was suggested to them that no change in their powers of taste could possibly have followed their operations:—

(1) One woman said that her doctor was giving her a medicine with a nasty taste, she took this on the anæsthetic side of the tongue and she did not taste it until it reached the back of the throat.

(2) A woman fond of sweets said she could taste an acid drop on the sensitive side of the tongue only.

(3) A man whose tongue was bilaterally anæsthetic in its anterior two-thirds, said that he used to salt his porridge very heavily at first, but soon had to cut it down, because, when the porridge reached the back of his throat, it produced an unpleasantly salty sensation.

Discussion.

From the historical section it will be seen that not only in the past, but in the present century, neurologists and neuro-surgeons have expressed many conflicting views on the changes in taste following trigeminal denervation of the mouth. Dandy (1930) stated categorically that no change follows trigeminal root section, whereas Harris believed that changes are usual and that they are permanent when the third division or Gasserian ganglion are destroyed with alcohol. It seems difficult to reconcile two views so diametrically opposed; there must be some reason for this divergence of opinion and it is of interest to inquire what this may be.

The physiological mechanisms of buccal taste are best set into action with the tongue inside the mouth, with the lips closed and with the substance freely washed with saliva pressed firmly against the palate. Until these conditions are satisfied it is difficult to analyse the finer appreciation and discrimination of taste. In the usual tests with the tongue in the

extruded position the conditions are abnormal and if the time factor is used as the only measure of gustatory change the cruder losses only are found and the more delicate changes are likely to be overlooked. This fact was realized very early in the present study and so was given particular consideration in the assessment of the results. When the patient first discovers that one side of the tongue is numb he is apt to assume that sense of taste has also gone from the anæsthetic area and gives his answers accordingly. Therefore, it was deemed advisable to explain the anatomical problem to each patient before his opinion was finally accepted; if this had not been done a far greater number would have been found in the group of complete loss immediately following operation.

There is no doubt in the author's opinion that trigeminal denervation of the tongue and mouth does affect the powers of buccal taste but more particularly in a discriminating way than as an absolute loss. These discriminative changes are more definite when both the 3rd and 2nd divisions are affected than when the 3rd division alone is blocked, an observation which very clearly demonstrates the importance of the soft palate as a receptor of gustatory stimuli.

Dandy, by a series of precise neurectomies in the posterior fossa, has proved beyond doubt that the glossopharyngeal nerve and the pars intermedia Wrisbergii are the anatomical pathways of buccal taste; when these nerves are severed the power to appreciate the tastes of salt, sour, bitter, sweet disappears absolutely.

It seems strange that trigeminal denervation should affect the sense of buccal taste, as it certainly does, when the 5th nerve is not one of the gustatory pathways. The changes in taste in the large majority of cases cannot be accounted for by damage to the great superficial petrosal nerve because they are present after the trigeminal root has been divided in the posterior fossa where the great superficial petrosal nerve is far from possible injury. Moreover, in those cases where the great superficial nerve was severed deliberately the gustatory changes were no more pronounced than in those cases in which it was conserved. The petrosal route for the taste fibres from the anterior two-thirds of the tongue may account for loss of taste in some cases but it has to be realized that this alternative route is rare whereas the impairment of taste following trigeminal denervation of the mouth is usual. As the gustatory pathways do not pass through the posterior root of the trigeminal nerve and as the changes in taste cannot always be accounted for by injury to the great superficial petrosal nerve there must be some other reason to account for the gustatory loss following trigeminal denervation.

The loss of feeling in an anæsthetic face is objective only; subjectively the face is full of feeling; numbness is a very outspoken sensation indeed, it embraces at least two components, coldness and swelling, and the feeling of swelling may be so dominant that it may be difficult to persuade the patient that there is no visible or palpable swelling. There is a decidedly unpleasant quality in the sensation of numbness and if not exchanged for that of painlessness the patients complain bitterly; a numb painful face is more unpleasant than a sensitive painful face.

It is unlikely that the sensation of numbness is due to stimuli arising in the severed nerve because pain would almost certainly be present if the cut proximal end were generating impulses. The sensation of pain is always absent following root section in cases of tic douloureux. It may be objected that impulses arising in the cut proximal end of the nerve do not give rise to the same sensations as run up the nerve when it is in connection with its receptors. The argument can be settled with some certainty when operating under local anæsthesia as any stimulation of the proximal nerve fibres causes a sensation of pain and not one of numbness. Moreover, a sense of numbness is caused irrespective of the method used for blocking the nerve impulses whether it be section, injection of alcohol or destruction of the nerve fibres by a diathermy current. It is improbable that such different local interferences with the nerve would initiate identical stimuli.

When the trigeminal nerve is cut the face is not completely denervated, there still remain intact the facial nerve, the autonomic nerves and the hypoglossal nerve. The sense of numbness may be due to sensations arising in the autonomic system or in the mechanisms of deep sensibility. Numbness, however, is still present when the facial nerve is out of action and is not removed by stellate ganglionectomy.

Normal sensation most likely is the summation or integration of all sensations normally coming from the face; if one modality is removed, then, even though each of the remaining modalities of sensation remains intrinsically unaltered they will not be able to stimulate the sensorium in the normal way. It may be suggested, therefore, in interpreting the changes in sensation of taste, that there is a readaptation of the higher centres to a new and unaccustomed combination of sensory impulses. In the case in question the taste impulses lack the background of common sensations.

III.—The Innervation of the Cornea.

Marshall (1931), after reviewing Jefferson's cases of fractional root section, came to the conclusion that the cornea had a dual nerve supply, the upper half being supplied by the ophthalmic division and the lower half by the

maxillary division of the 5th nerve. The observations on the present series do not confirm this view. In four cases of intracranial section of the maxillary nerve at the foramen rotundum the upper boundary of anæsthesia skirted the rim of the lower eyelid and in no case did it encroach on the cornea. To confirm this finding a clean anatomical severance of the ophthalmic fibres was necessary. This section was carried out successfully on a suitable case, in which the pain was limited to the forehead, after intracranial reflection of the dura mater upwards from the margin of the sphenoidal fissure. The whole of the cornea was rendered insensitive by the neurotomy and it is believed that this is the first time this observation has been made in man.

Whether the cornea is supplied by pain fibres alone has long been a subject of discussion amongst anatomists and neurologists and until a small series of five patients had been operated on by the Sjöqvist technique a confident opinion could not be expressed on this neuro-anatomical problem. In the Sjöqvist operation the descending fibres of the trigeminal tract are divided in the medulla oblongata at the level of the first vagal root; this method of tractotomy renders the face analgesic, sensibility to light touch being impaired to a slight degree only. In two cases in which the section had been carried out with precision the cornea was completely insensitive to all kinds of painful stimuli but appreciated the stimulus of a wisp of wool, or the touch of a fine camel hair brush. Marshall also showed that the cornea was sensitive to light touch as well as to painful stimuli and in explanation suggested that the nature of the sensation aroused depended on the form of the stimulus, a sufficiently light one invoking the sense of light touch and a heavier one a sense of pain. This physiological explanation is unnecessary, since the dissociated anæsthesia produced by the trigeminal tractotomy offers a ready anatomical solution. The sense of touch is ordinarily in abeyance because it is overwhelmed by the sense of pain.

IV.—The Movements of the Tongue.

That the smooth co-ordination of the movements of the tongue depends in large measure on impulses mediated by the trigeminal pathways has been demonstrated by two cases of bilateral nerve section. In each case immediately following the second operation, the tongue became ataxic, it came forward between the teeth whenever the patient attempted to speak, enunciation of long words was uncertain and the tongue could not be held still in the position of protrusion. The ataxia improved considerably with time, although there had been no regeneration of the divided nerves. This probably indicates that, as in the facial nerve, there are also proprio-

ceptive fibres in the hypoglossal nerves, which though not so important as those in the trigeminal nerve, are able when necessary to function usefully. A considerable degree of compensation occurs, but is generally incomplete. The slight spitting of these patients in conversation and the slight difficulty of their enunciation suggest a loss of proprioceptive sensation.

V.—Changes Referable to the Sympathetic Nervous System.

Two methods for detecting interference with the sympathetic pathways in the face have been used, reflex sweating and the vascular tests. No temperature or colour change has ever been recorded in the anæsthetic skin following tractotomy, root section or intracranial neurectomy. They have been observed only when alcohol is being injected into the ganglion and were first commented on by Jefferson. The vessels in the conjunctiva dilate, the eyelids blush and the temperature rises about one degree on the galvanometric scale of the electrical thermometer. These changes do not necessarily indicate the presence of sympathetic fibres in the ganglion, though that may do so; they could be explained by the diffusion of alcohol on to the neighbouring sympathetic fibres around the carotid artery. One experience in a recent case rather favours this view, as shortly after the blush of the eyelids a transient 3rd nerve palsy developed, showing that diffusion of the alcohol was taking place. The flush can, however, be observed in cases where no extraganglionic complications occur.

The sweating tests have been studied in some detail. List and Peet were the first to carry out these tests after trigeminal denervation and they came to the conclusion that few or no sympathetic fibres join the trigeminal pathways within the cranial cavity, but that extracranially a rich supply of sympathetic fibres is given to the various trigeminal branches from the periarterial plexuses on the large vessels in the vicinity. List and Peet's intracranial sections are precise but their extracranial experiments necessarily lack precision and so are open to criticism. It is scarcely possible to resect or block the supra-orbital nerve without damaging such neighbouring structures as vascular plexuses. Neurectomy necessitates a fair sized incision and one can never be sure that an injection of alcohol into so small a nerve as the orbital remains entirely intraneural. In two cases in which a considerable length of the supra-orbital nerve had been avulsed several months previous to the test, and the forehead was still numb, the reflex sweating reactions were equal on both sides. It seems strange that if the main sympathetic pathways run in this nerve they should have made so complete a recovery as shown in these two cases. The results in the present series have not been so clear cut as those of List and

Peet. For instance, in one case it was impossible to make either the denervated side or the fully sensitive side of the face sweat even though the rest of the body and arms were sweating profusely. Also in some cases of posterior root section the sweating has been much more patchy on the operated than on the unoperated side; in the lateral extradural approach this might be accounted for by damage to sympathetic fibres outside the trigeminal root but similar differences have occurred in one case of root section through the posterior fossa where this possibility can be eliminated. What is certain, however, is that sympathetic fibres in any bulk do not enter the intracranial trigeminal pathways and in no case of tractotomy were the sweating reactions diminished. This indicates that sympathetic fibres are not present in the caudal parts of the trigeminal tract. Alternatively, there is no clear evidence that the sympathetic fibres follow accurately the peripheral branches of the trigeminal nerve.

VI.—The Great Superficial Petrosal Nerve: The Ætiology of Paralytic Interstitial Keratitis.

One of the most serious complications following ganglion block or root section is the development of paralytic interstitial keratitis. Recently, it has been suggested that the essential cause of keratitis is a dry eye, that is, the absence of tear secretion. This view is gaining ground and is influencing the mode of treatment. The anatomical pathway generally accepted for secretory nerves to the lachrymal gland is circuitous. The great superficial petrosal nerve leaves the geniculate ganglion of the facial nerve to enter the middle fossa via the hiatus fallopii, it is then joined by the deep petrosal nerves from the sympathetic plexus on the carotid artery to form the vidian nerve. This dual nerve traverses the vidian canal to enter Meckel's ganglion and from here a secretory nerve passes to the lachrymal gland via the temporo-malar branch of the second division of the trigeminal nerve.

As the dura mater is swept from the floor of the middle fossa in the operative extradural approach to the trigeminal root, the great superficial petrosal nerve is seen lying on the tip of the petrous bone and it is part of the operation to separate by sharp dissection the nerve from the dural envelope to which it is firmly attached. It can be appreciated how easily the nerve may be injured and how easily suppression of tears be produced. If a dry eye be the cause of corneal ulceration, then the essential cause of keratitis is injury to the great superficial petrosal nerve. The method of separation of the great superficial petrosal nerve from the dura is the same in all middle fossa operations and so the nerve is exposed to the same

dangers of injury in fractional as in complete root section. As a result it must frequently be out of action in those cases in which corneal sensation is spared and yet we have never seen keratitis when the cornea remained sensitive. There is ample clinical support for the view that the essential ætiological factor of keratitis cannot be paralysis of tear secretion alone. Many of our cases have a tearless eye on the operated side with a healthy cornea. In one case operated on by the Sjöqvist technique a transient keratitis developed in an analgesic eye in which tear secretion was normal. The only constant finding in keratitis is analgesia of the cornea and there

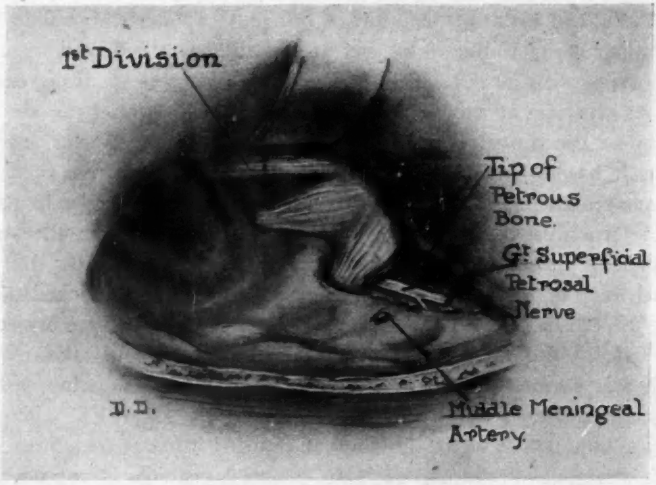

FIG. 5.—Drawing by Miss Davison to show the position of the great superficial petrosal nerve in relation to the floor of the middle fossa and to the Gasserian ganglion after the dura mater has been dissected upwards in the lateral approach to the posterior trigeminal root. Anteriorly the dissection has been carried unusually high ; this was done to expose the ophthalmic fibres. The plane in which they were severed is shown.

is convincing evidence that the principal factor in its production is trauma acting on an insensitive membrane. Certainly it was the oft-repeated attempts at elicitation of the corneal reflex in the tractotomy case which caused the corneal changes because as we ceased to apply the stimulus the condition improved and keratitis did not develop in the opposite eye, even though the corneal reflex had been elicited in the same way and on the same number of occasions. Tarsorrhaphy invariably cures or arrests the keratitis and it may recur on division of the synechiæ even though an interval of a year or two has elapsed since suture. The factor of infection

is apt to be overlooked and this is a grave danger. It must be the experience of every one that a pre-operative "bad eye" is particularly liable to be affected.

In addition to the clinical observations recorded above, experiments have been made in the course of section of the trigeminal root in the middle fossa. The great superficial petrosal nerve has been stimulated with a faradic battery on two occasions, it has been blocked once with alcohol and three times it has been divided with a scalpel. Faradic stimulation caused no marked increase in secretion of tears either early or late. In the cases of severance of the nerve tear secretion has later been stimulated emotionally and by the inhalation of pungent vapours (those from fresh horse-radish being found most useful) and the tears collected by a wisp of wool lying with its tail within the palpable fissure at the inner canthus. A serious criticism of this method of collecting tears is that the absorbent material in the sensitive eye is an adequate stimulus to tear secretion, whereas it has no such stimulatory action on the insensitive eye and so the measurement by weight, though theoretically more precise, is perhaps no more trustworthy than those of direct observation when the changes are sufficiently obvious. The results of these experiments show that when the pathways of the great superficial petrosal nerve are blocked or completely severed the secretory powers of the lachrymal gland are not entirely in abeyance, some other mechanism, probably a local one, takes over and though tear secretion is far from the normal the eye coverings are kept adequately moist.

In the final review of the ætiology of keratitis it has to be admitted that though analgesia of the cornea is an essential primary factor no case in which the coverings of the eye have remained healthy has ever been completely dry in spite of the absence of obvious tear secretion. To prove the essential part played by the lachrymal gland it is necessary to observe a completely dry eye with a normally sensitive cornea. Unfortunately it has not been possible to produce this combination and no record of one can be found.

Test No. 1.—Fractional Section by the Lateral Extradural Approach of the Upper Two-thirds of the Trigeminal Root with sparing of the Mandibular Fibres.

The great superficial petrosal nerve was dissected free from the dura mater and then severed with a scalpel. The cornea and conjunctiva were completely anæsthetic.

Result :—	R. Operated side	L. Normal eye
Weight of wool	0·1300 grammes	0·1275 grammes
Weight of wool + tears	0·1315 „	0·2850 „
Weight of tears in grammes collected in ½ hour	0·0015 „	0·1575 „

Comment.—In this case the insensitive cornea was perfectly healthy; it was moist but tear secretion was absent; free tear secretion was present in the sensitive eye.

When tears were made to secrete by emotional stimuli they welled into the sensitive eye, but few could be seen in the denervated eye. Before operation tear secretion was equal in both eyes.

Test No. 2.—Fractional Section by the Lateral Extradural Approach of the Lower Two-thirds of the Trigeminal Root with sparing of the Ophthalmic Fibres. The great superficial petrosal nerve was defined and then severed with a scalpel.

Result :—	R. Operated side	L. Normal eye
Weight of wool	0·2204 grammes	0·2010 grammes
Weight of wool + tears	0·2224 ,,	0·2126 ,,
Weight of tears in grammes collected in ½ hour	0·0020 ,,	0·0116 ,,

Comment.—The cornea and conjunctiva were healthy. The coverings of the eye were moist. Tear secretion was diminished.

Test No. 3.—The whole trigeminal root was severed by the lateral extradural approach and the great superficial nerve divided by a scalpel. The cornea and conjunctiva were completely anæsthetic.

Result :—	R. Operated side	L. Normal eye
Weight of wool	0·2100 grammes	0·2175 grammes
Weight of wool + tears	0·2175 ,,	0·3900 ,,
Weight of tears in grammes collected in ½ hour	0·0075 ,,	0·1725 ,,

Comment.—The insensitive cornea was perfectly health; the coverings of the eye were moist but tear secretion was diminished. Before operation tear secretion was equal on both sides.

Conclusion.—The great superficial petrosal nerve is a mixed nerve, the afferent fibres being probably gustatory to the palate and the efferent fibres being secretory motor at least to the eye and nose.

The above section is a preliminary note on work which is being done on the anatomy and function of the nerve and further results will be published later. I would like to thank Mr. Jefferson for the generous use of his material and for his criticisms and help in the production of this paper.

BIBLIOGRAPHY.

BERNARD, C. (1843), "On the Alteration of the Taste in Paralysis of the Facial Nerve," Thomas Richmond.

——(1858), "Leçon du Système Nerveux." Paris, p. 192.

CARMICHAEL, A. E., and WOOLLARD, H. H. (1933), *Brain*, **56**, 109.

CUSHING, H. (1903), *Bull. Johns Hopk. Univ.*, **14**, 71.

DAVIES, M. H. (1907), *Brain*, **2**, 219.

DIXON, F. A. (1897), *Edin. med. J.*, **1**, 395.

GOWERS, W. R. (1885), "Lectures on the Diagnosis of the Brain." London.
HARRIS, W. (1926), "Neuritis and Neuralgia." Oxf. Univ. Press, p. 247.
HARTLEY, F. (1892), *N. Y. med. J.*, **55**, 317.
JEFFERSON, G. (1931), *Brit. med. J.*, **2**, 879.
KOSTER, G. (1900), *Dtsch. Arch. klin. Med.*, **68**, 343 and 505.
——(1904), *Münch. med. Wschr.*, **51**, 333 and 392.
KRAUSE, F. (1896), "Die Neuralgie des Trigeminus." Leipzig, p. 103.
——(1892), *Verh. dtsch. Ges. Chir.*, **21**, 199.
——(1892), *Arch. klin. Chir.*, **44**, 821.
——(1895), *Münch. med. Wschr.*, **42**, 577, 602, 628.
LEWIS, D., and DANDY, W. E., (1930), *Arch. Surg.*, **21**, 249.
LUSSANA, P. (1872), *Arch. de Physiol.*, **2**, 20 and 197; **4**, 150 and 334.
——(1869), "Recherches sur les nerfs du goût Paris."
MAGENDIE, F. (1822), "Précis élémentaire de Physiologie," John Revere. Baltimore.
MARSHALL, E. N. (1931), "The Sensory Functions of the Trigeminal and Facial Nerves with Special Reference to Deep Sensibility of the Face and the Innervation and Sensibility of the Cornea," M.D. Thesis, University, Manchester.
NAGEOTTE, J. (1906), *Rev. Neurol. Psychiat.*, **4**, 472.
ROWBOTHAM, G. F. (1938), *Brit. med. J.*, **2**, 1073.
SCHIFF, M. (1896), "Gesammelte Beiträge zür Physiologie," **3**, 183.
SCHWARTZ, H. G., and WEDDELL, G. (1938), *Brain*, **61**, 99.
SMYTH, G. G. E. (1938), "The Spinal Tract of the Trigeminal Nerve and its Central Connections," M.D. Thesis, Victoria University, Manchester.
STOPFORD, J. S. B. (1930), "Sensation and the Sensory Pathway." London.
WAKELEY, P. G., and MULVANEY, J. H. (1939), *Lancet*, April 1, 746.
ZIEHL, F. (1889), *Virchow's Arch.*, **117**, 52.

THE CONGENITAL FACIAL DIPLEGIA SYNDROME: CLINICAL FEATURES, PATHOLOGY AND ÆTIOLOGY.[1]

A Review of Sixty-one Cases

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Congenital paralysis of cranial nerves is sufficiently rare to attract special attention. The ocular and facial nerves are those most frequently affected and the anatomical relationships of the latter render them susceptible to paralysis from a greater variety of causes. Thus, there are several types of congenital facial palsy. The intra-partum types predominate and, with the extremely rare exception of bilateral peripheral trauma, they are all unilateral. Of the ante-partum types, however, the bilateral variety is the commonest and is usually associated with other cranial nerve palsies. This paper is solely concerned with the ante-partum bilateral type.

A child displaying many typical features of the condition was seen recently at the Royal Edinburgh Hospital for Sick Children. Perusal of the relevant literature showed that no adequate review of the published cases had ever been undertaken ; German literature proved to be the most fruitful, while British literature contained brief accounts of only six cases. An analysis of the clinical and other features of this remarkable congenital syndrome may, therefore, be of interest.

Case Report.

E. O., female, aged 1 year 10 months.

History.—The parents, a sister aged 12 and a brother aged 8, are healthy. The pregnancy was normal. Spontaneous delivery followed an uneventful labour lasting nine hours. The birth weight was about eight pounds. A peculiar facial appearance, bilateral convergent strabismus and club-foot were all noticed shortly after birth by the doctor in attendance. The baby apparently nursed quite well, although her mother maintains that she did not nurse as well as her other children. She was weaned when two months old. There was never any dysphagia nor nasal regurgitation.

The patient first came under observation at the age of 5 months, her mother complaining that she had never smiled nor moved her face—even when laughing and crying. During the first few weeks she thought the infant had a film over

[1] Based upon a thesis accepted for the degree of M.D.Edin., July, 1938.

her eyes and that she was blind. She did not seem to take notice until she was 3 months old. When first seen the infant was well nourished and displayed an immobile, expressionless face, a severe degree of bilateral convergent strabismus and a partially corrected talipes equino-varus on both sides. There was no ptosis and the eyes were not completely closed during sleep.

As the child grew older the eyelids became more nearly approximated during sleep, and a slight but definite amelioration of the squint was observed. Recently,

FIG. 1.—E. O., aged 1 year and 5 months.

while eating, she had been observed to dislodge food from the cheeks with her hands. Early doubts about the mental state were soon dispelled as the child grew older. Orthopædic measures, begun soon after birth, effected a great improvement in the position of the feet. Dentition began at 5 months. Apart from a recent mild attack of bronchitis the general health has been good.

Physical examination.—A healthy looking, well-developed female child. The forehead is tower-shaped and somewhat flattened towards the sides; the fontanelle is almost closed. The cheeks are plump and the peri-orbital regions rather hollow.

FIG. 2.—E. O., aged 3 years. "Smile" showing the contraction at the left corner of the mouth.

FIG. 3.—E. O., aged 3 years. Crying.

There is bilateral epicanthus. The base of the nose is broad and the lower part has a squarish appearance owing to the palsied alæ nasi. The mouth is always slightly open and the upper lip prominent ; during sleep it is opened more widely and assumes a triangular shape. The uvula is normal. The ears have a normal shape. There is no malformation of the pectoral or mammary regions. The only deformity of the limbs is the bilateral talipes equino-varus. The mental development and behaviour are normal.

Cranial nerves.—The 3rd, 4th and 6th nerves: When looking at objects the head is moved in the direction of vision, whether horizontal or vertical, and it is usually tilted to one or other side. I am indebted to Dr. J. R. Paterson, Hon. Ophthalmic Surgeon to the Royal Edinburgh Hospital for Sick Children, for the following report on the condition of the eyes:—

"There is a severe degree of convergent strabismus in both eyes. The only definite movement that can be elicited is the involuntary upward movement of the eye on the child attempting to close the lids. It would, therefore, appear that the superior rectus is still functioning in both eyes, certainly as far as this synergic movement is concerned. There is no ptosis, indicating normal action of the levatores palpebrarum ; the lids are now approximated during sleep. The pupils are normal in size, shape and reactions. The fundi show no abnormality whatever."

The 7th nerve: The face is immobile and expressionless at all times, indicating complete facial diplegia (fig. 1). There are no wrinkles in the skin of the face or forehead. Winking is slow and feeble and there is a moderate degree of epiphora. A little dribbling occurs from the corners of the mouth. Crying produces a whining noise with the usual interjections, and laughter a series of short, pleasant phonations. The former is accompanied by flushing of the face, but there is no facial movement in either. The vocabulary consists of only a few simple words and enunciation is hampered by the labial palsy. No response of the facial muscles to either faradism or galvanism could be obtained, but the child's nervousness rendered accurate testing of the muscles impracticable.

Other motor nerves: There is no evidence of paresis in the muscles of mastication or in the soft palate, pharynx or larynx. The child cannot be induced to protrude the tongue beyond the lips, but there are no signs of lingual atrophy or palsy or of fibrillary twitching.

Sensory nerves: There is no apparent impairment of any of the sensory functions.

There are no other demonstrable abnormalities of the nervous system.

Other systems.—The thoracic and abdominal organs appear healthy.

X-ray examination: The skull has a tower-shaped frontal region, but is otherwise normal. The vertebral column is normal.

Blood Wassermann: Negative.

Further examination.—Aged 3 years 1 month.

The parents first noticed a slight movement of the left corner of the mouth when the child was 2½ years old, and they maintain that its amplitude has increased. She often "smiles" when asked to do so and the parents' observation is easily confirmed. The movement is small but is accompanied by considerable wrinkling of the skin infero-lateral to the left side of the lower lip (figs. 2 and 3). No other facial movement is discernible.

There is no longer any doubt about the condition of the lingual muscles as the tongue is frequently well protruded and has a normal appearance. The con-

dition of the eyes is unchanged. The position of the feet has become worse owing to neglect.

The child is running about and has an attractive, friendly manner. Although she did not walk alone or speak freely until she was 2½ years old there is no question of any mental defect. Her vocabulary is good but it is difficult for strangers to understand much of what she says owing to the poor enunciation.

Summary.—Congenital facial diplegia, incomplete in left lower quadrant. Congenital ophthalmoplegia externa, bilateral, partial. Congenital talipes equino-varus, bilateral.

Clinical Features.

Since von Graefe described a case of congenital facial diplegia in 1880 some sixty examples of this anomaly have been recorded, and these, including the present one, have been tabulated in chronological order in Table I (pp. 386-8) where the principal clinical features have been indicated symbolically in each instance. The incidence of these features has been shown schematically in Table II (p. 389).

The facial diplegia is usually accompanied by palsies of other cranial nerves—particularly the ocular. The abducens nerves are affected in a high percentage of cases, the hypoglossal and oculo-motor nerves only in a minority. All these congenital palsies are, of course, stationary from birth. The high incidence of congenital deformities is also a striking feature: the chief of these is club-foot, while brachial deformity and pectoralis muscle hypoplasia have been observed on numerous occasions. Other malformations of a minor nature are frequently encountered. This outline of the principal features will now be followed by their individual consideration.

The facial diplegia.—The facial palsy was usually observed during the first few days of life owing to difficulty with nursing and incomplete closure of the eyelids during sleep. Quite often, however, it was not noticed for a few weeks or months, until the inability to smile or the lack of facial movement on crying aroused the parents' concern. The most arresting feature of the facial palsy was, of course, the mask-like face which was most noticeable during laughing and crying. Because of this immobility the face and forehead were devoid of wrinkles, but it was exceptional for the subcutaneous tissue or the skin of the face to appear "atrophic."

It is interesting that in some cases, as in the present one, a slight diminution in the width of the palpebral fissures during sleep was noticed as infancy advanced. Lagophthalmos was, of course, another feature and the principal cause of the incomplete palpebral closure. The puncta lachrymalia were frequently slightly everted, thus accentuating the

TABLE I.—PUBLISHED CASES OF CONGENITAL FACIAL DIPLEGIA SHOWING THEIR SALIENT CLINICAL FEATURES.

Case No.	Year	Authors	Sex	Age	Facial palsy, distribution ● = Complete	Abducens palsy		Convergent strabismus	Ophthalmoplegia externa		Ptosis	Trigeminal palsy		Lingual palsy		Mental defect	Club-foot		Brachial malformation		Pectoralis muscle defect		Other malformations, &c.
					R. L.	R.	L.		R.	L.		R.	L.	R.	L.		R.	L.	R.	L.	R.	L.	
1	1880	v. Graefe	M.	20	● ●	+	+																Epilepsy
2	1881	Harlan	M.	18	● ●	+	+	+															
3	1882	Chisolm	F.	35	● ●	+	+	+															Aplastic lachrymal caruncles
4	1888	Moebius	M.	50	● ●	+	+												+				
5	1889	Schapringer	F.	8	● ●	+	+					+		+						+			Hypoplastic lachrymal caruncles. Bifid uvula. Epicanthus
6	1891	Bloch	M.	9/12	●	+	+										+	+					"Other abnormalities"
7	1892	Fryer	M.	16	● ●	+	+												+				
8	1895	Kirmisson	M.	7	● ●												+	+					
9	1896	Procopovici	M.	18	●																		
10	„	„	F.	7	●	+	+	+															Epicanthus
11	1897	Schmidt	M.	6	● ●	+	+	+						+	+							+	
12	1898	Thomas	M.	21	● ●																		Ear deformity. Deafness
13	„	„	M.	19	● ●																		Ear deformity. Deafness
14	1900	Heubner	M.	1 7/12	● ●	+	+	+							÷								No tear secretion
15	1901	Bernhardt	M.	10/12	● ●																		
16	1902	Köster	M.	?	● ●																		Ear deformity. Complete facial anhidrosis
17	„	„	M.	?	● ●																		Ear deformity. Complete facial anhidrosis
18	„	Decroly	M.	7/12	● ●				+	+													
19	„	Taylor	M.	15	● ●						+												
20	1903	Rainy and Fowler	F.	10/12	● ●																		

21	1905	Batten	?	9	?	+	+							+	+										
22	„	Gierlich	F.	14		+	+	+							+										
23	„	Gützmann	M.	12		+	+											+	+	+					Hypoplastic mammæ. "Other abnormalities"
24	1908	Ziehen	M.	18		+	+		+	+	+			+	+							+			
25	1909	Collins	?	?	?	+	+		+	+					+							+			
26	1910	Lennon	M.	2		+	+	+	+	+								+	+						
27	„	„	M.	14		+	+	+	+	+								+	+						
28	1912	Peritz	M.	?	?	+	+									+						+			
29	„	Welde	F.	2½		+	+	+						+	+	+									
30	1913	v. Pfaundler	?	1/12	?	+	+							+				+							
31	„	Beetz	F.	22																		+			Ear deformity. Congenital dislocation of hip
32	„	„	M.	20		+				+	+	+				+									Ear deformity. Multiple bilateral defects of scapular muscles
33	„	„	F.	7			+																		Ear deformity
34	1915	Snowball	F.	11		+	+	+																	
35	1916	Kahlmeter	M.	38					+	+						+									Infantilism
36	1917	Gütermann	M.	7/12		+	+	+						+						+		+			Hypoplastic lachrymal caruncles. Epicanthus
37	1918	Fry	?	11/12																					
38	1919	Fry and Kasak	F.	11		+	+		+	+		+	+	+	+						+		+		
39	1921	Abrahamson	F.	4		+	+								+										Epilepsy
40	1922	Cadwalader	F.	13																					Deafness
41	„	„	F.	10		+	+	+																	
42	1923	Kirby	M.	52		+	+							+	+			+							
43	1924	Cameron	M.	3		+	+		+	+								+	+	+					
44	1927	Van Gelder and Weyl	M.	53		+	+		+	+	+	+	+	+						+	+				Ear deformity

TABLE I.—PUBLISHED CASES OF CONGENITAL FACIAL DIPLEGIA, &c.—*Continued.*

Case No.	Year	Authors	Sex	Age	Facial palsy, distribution ● = Complete R. L.	Abducens palsy R. L.	Convergent strabismus	Ophthalmoplegia externa R. L.	Ptosis	Trigeminal palsy R. L.	Lingua palsy R. L.	Mental defect	Club-foot R. L.	Brachial malformation R. L.	Pectoralis muscle defect R. L.	Other malformations, &c.
45	1928	Mandels	M.	15	?	+ +	+	+ +				+		+	+	
46	1929	Bonar and Owens	M.	9/12	●●				+				+			Epicanthus
47	1930	Alajouanine, Huc and Gopcevitch	F.	6	●+	+ +	+						+ +	+		
48	„	„	F.	5	+●	+ +	+				+ +		+ +			
49	„	„	M.	1 9/12	●●	+ +	+						+ +			
50	„	„	F.	4/12	●●	+ +	+						+ +			
51	„	Ullrich	F.	8	+				+							Hypoplastic mammæ. Pterygium colli
52	1931	Yealland	F.	16	+	+ +		+ +			+ +					
53	„	Spatz and Ullrich	M.	3/12	+●	+ +		+ +						+		Hyperthelia
54	„	Allen	M.	10	●●	+ +		+ +					+ +	+ +		Hydrocephalus. Epilepsy
55	1932	Bielschowsky	F.	9	●●	+ +										
56	„	Garrahan and Cucullú	M.	2	●●	+ +	+						+ +			
57	„	„	F.	3/12	●●	+ +	+				+ +		+ +	+		Bifid uvula. Epicanthus
58	„	Babonneix and Migel	F.	5	+●	+ +	+	+ +			+ +					
59	1933	Gareiso and Barbieri	F.	5	●●	+ +	+					+	+ +			
60	1935	Decourt and Perreau	M.	9	+●	+ +	+						+ +			
61	1939	Author's case	F.	3 1/12	●●	+ +	+	+ +					+ +			Epicanthus
						45	23	15	6	4	18	6	19	13	8	

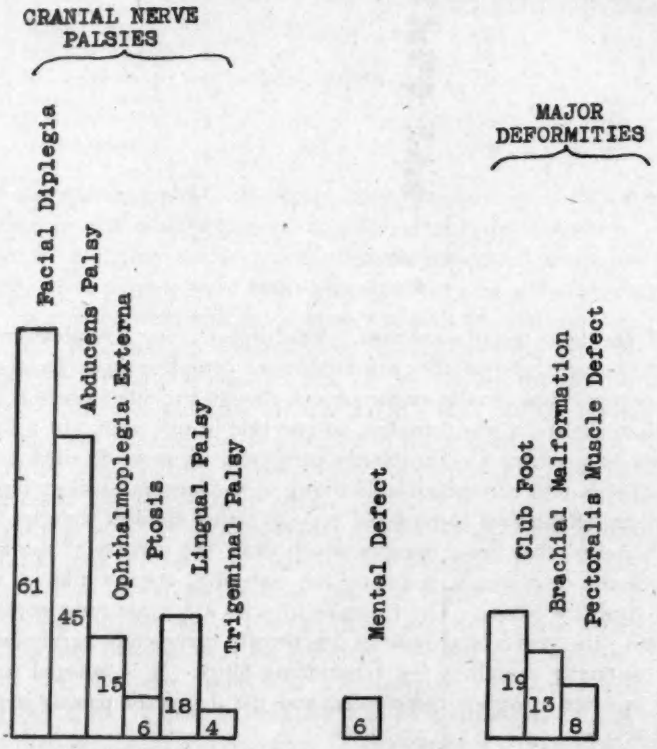
The following cases were inadequately authenticated for inclusion, but appeared to be genuine: Procopovici (1896), Treacher Collins (1915), Cadwalader (1922), Ullrich (1930), Errecart (1930).

The facial diplegia appears to have been acquired in the cases published by Recken (1891) and Bach (1893).

epiphora which was an almost constant feature. In older patients ectropion was apt to occur.

Inability to suckle in infancy has already been alluded to: the difficulty may be only slight, but it was often noticed that the nipple or teat was drawn further into the mouth than usual. Inability to close the mouth

TABLE II.—INCIDENCE OF THE PRINCIPAL CLINICAL FEATURES.



was the rule. Undue prominence of the upper lip was a striking feature; in adults the lower lip was usually everted and prominent also. Dribbling of saliva was a troublesome symptom. Speech was nearly always indistinct owing to the inability to close the lips and thus make labial sounds, e.g. ā for ma, ă for map. While eating, food was apt to lodge in the cheeks, as in the present case.

The degree and distribution of the palsy have been analysed in

fifty-six cases, five being discounted owing to insufficient data. The palsy was incomplete in the majority of cases, but of severe degree in nearly all of them. Table III indicates the frequency of complete paralysis in

TABLE III.—DISTRIBUTION OF COMPLETE PARALYSIS IN THE VARIOUS FACIAL QUADRANTS.

R. L.	No. of cases
	19
	5
	4
	13
	1
	3
	1
	10
Not stated	5

● = Complete palsy.

each of the four facial quadrants. The diplegia was complete in one-third of the cases, and another third exhibited complete upper facial palsy. When partial it was usually asymmetrical, though the difference was rarely more than slight; it was complete on one side in ten cases. In a further ten cases no quadrant was completely paralysed. A more detailed analysis of the distribution is impracticable owing to the custom of describing the movements of the face in terms of regions rather than of muscles. It is clear, however, that those muscles which draw the corners of the mouth outwards and downwards, including the platysmæ, are the muscles which most frequently escape. The frontalis muscles are those most constantly paralysed; the peri-orbital muscles are usually completely paralysed also, but occasionally contain a few functioning fibres. It is unusual for any of the muscles to escape completely, and the degree of paresis is nearly always severe.

The electrical reactions of the facial muscles were tested in twenty-three cases. There were no qualitative changes in the paretic muscles but a diminished reaction was invariable.

The characteristic distribution of the palsy contrasts sharply with that of the common supranuclear and infranuclear types, and it may be of diagnostic value in the absence of the other features of the syndrome.

Only ten cases of the sixty-one were uncomplicated by other cranial nerve palsies, and it may be significant that deformities of the limbs

seldom occurred in this group. The incidence of the principal features in this group is contrasted with that in the "complicated" group in Table IV. The features of the facial palsy are usually similar in both groups.

TABLE IV.—THE CONTRASTING FEATURES OF "COMPLICATED" AND "PURE" FACIAL DIPLEGIA.

	Other cranial nerve palsies	No other cranial nerve palsies
Number of cases	51	10
Major deformities	28	1
Minor deformities only, excluding auricular	7	0
Auricular deformity	4	4
Deafness	0	3
Mental defect	6	0

Ocular manifestations.—In those with convergent strabismus the ocular abnormality was usually noticed at birth or shortly afterwards. In the absence of a squint, ocular palsies sometimes escaped notice until later infancy. The parents were often concerned by the white appearance of the eyes seen between the incompletely closed lids during sleep. This appearance is sometimes attributed to "a film over the eyes" as in the present case. A slight amelioration of the convergent strabismus was observed in three of the cases of Alajouanine, Huc and Gopcevitch (1930) and I am quite satisfied that it occurred in the present case also.

External ocular palsies, including ptosis, accompanied the facial diplegia in fifty cases—five-sixths of the total.

Abducens paralysis occurred in no fewer than forty-five patients, thus constituting one of the most characteristic features of the syndrome; it was bilateral in all except two cases and was usually complete. Abducens paralysis was the only ocular palsy in thirty-one cases; it was accompanied by oculo-motor palsy in thirteen instances. Twenty-three—almost exactly half—of the abducens group had a convergent strabismus which was usually bilateral. It may be recalled here that strabismus is the rule in the acquired form of 6th nerve palsy. The absence of strabismus is usually associated with paresis of the medial recti muscles.

External ophthalmoplegia occurred in fifteen cases and was always bilateral; it was usually severe but rarely complete—it was thought to be complete in the infant described by Spatz and Ullrich (1931). Internal ophthalmoplegia has never been observed.

Ptosis occurred in six cases; it was usually only partial, but it was bilateral in each instance. In three cases it was the only ocular palsy to accompany the facial diplegia, in another it complicated a slight unilateral

abducens paresis, while in the remaining two cases it was associated with ophthalmoplegia externa.

Trochlear involvement has seldom been referred to in the literature, probably owing to the difficulty of assessing it—especially in children—but this nerve is liable to be affected along with the oculo-motor nerve as demonstrated histologically by Spatz and Ullrich in their case.

Amblyopia was not a feature of these cases, but refractive errors and astigmatism frequently occurred.

Owing to the feebleness of winking and the incomplete closure of the eyelids during sleep the corneæ and the conjunctivæ are poorly protected, and recurrent or chronic conjunctivitis frequently occurs. Corneal opacities are unusual but are sometimes seen in adult patients.

Lingual features.—Paresis and hypoplasia of the tongue occurred in eighteen cases and was always associated with ocular palsy. It involved both sides in ten cases but was rarely symmetrical. Fibrillary twitchings of the tongue were noted in two instances, but no significance can be attached to them in view of the static condition of the lingual and other palsies from birth. The dysarthria and the difficulty in moving food about the mouth were accentuated by lingual involvement.

Trigeminal palsy.—It was unusual for the muscles of mastication to be affected, but in four cases masticatory difficulty was encountered. It affected both sides in three of them but was never severe. The striking feature was the restriction of lateral chewing movements.

Paresis of the soft palate.—In many of the cases no reference was made to the throat, presumably indicating normal findings in most of them. There were four instances of bilateral paresis of the soft palate, six of dysphagia—in three of which it recovered in infancy—and four of nasal regurgitation in infancy. Three of the cases with dysphagia and regurgitation had lingual palsy which probably contributed to the difficulty. In no case was there any evidence of gross vagal dysfunction: the nerves responsible for the paresis of the soft palate are distributed via the vagus nerve but originate in the accessory nuclei.

Club-foot.—The malformation occurred in nineteen cases—almost one-third of the total—and it was bilateral in sixteen instances. The deformity was one of talipes equino-varus in all cases except that of Kirmisson (1895) which had the usual deformity on the right side and a calcaneo-valgus deformity on the left. In most of these cases the deformity had been partially or wholly corrected in infancy. Other deformities of the foot, such as syndactyly, have never been recorded.

Pectoralis muscle defect.—Hypoplasia of the pectoralis muscles was a

feature in eight cases; it was always unilateral and associated with mammary hypoplasia of the same side. The condition was described in detail in only three cases and was typical of congenital defect of the pectoralis muscles. All three patients showed a complete absence of the sterno-costal part of the pectoralis major, while the clavicular part was only slightly affected or had escaped altogether; the pectoralis minor was absent in two cases and hypoplastic in the third. In the case described by Mandels (1928) the 3rd, 4th and 5th costal cartilages were defective, and the hypoplasia involved other muscles of the chest and arm on the corresponding side. The association of local skeletal anomalies with pectoralis muscle defect is not infrequent. In three cases there was brachial hypoplasia on the same side.

Mention may be made here of the unique case of Beetz (1913)—Case No. 32, a youth of 20 years whose pectoralis muscles did not appear defective, but who exhibited a hypoplasia of the serratus anterior, infraspinatus and latissimus dorsi muscles on both sides, and of the trapezius, levator scapulæ and supraspinatus muscles on the right side. The serratus anterior was completely absent on the right side and poorly developed on the left. Bilateral muscle defect is a very rare anomaly.

Malformation of the arm and hand.—Brachial malformation was encountered in thirteen cases, in twelve of which it was specified; it involved the arm in only four instances whereas the hand was always affected. There was one instance of congenital amputation of the hand and one of "club-hand," while in four cases the affected hand was "much smaller" than the other—syndactyly was a feature in two of these cases. In the six remaining cases the malformation was confined to the fingers; in two there were brachydactyly and syndactyly, in three others there was syndactyly alone, while another possessed a deformed index finger. The syndactyly was bilateral in two of the seven cases in which it occurred. Three of the four cases with brachial malformation exhibited pectoralis muscle defect on the same side, whereas none of the nine cases with hand involvement alone was so affected. The brachial dysplasia was associated with club-foot in five cases.

Minor congenital anomalies.—In a few instances these have been disposed of as "other abnormalities," but in the great majority they have been enumerated. In several cases the root of the nose was broad and rather flat. Bilateral epicanthus occurred in six cases, in two of which it was associated with hypoplastic lachrymal caruncles. Another case had aplastic lachrymal caruncles. There were eight instances of ear deformity; it was usually bilateral and confined to the lobe: two of the three deaf cases fall into this group. Arched palate was noted four times and bifid

uvula twice. In addition to those cases exhibiting pectoralis muscle defect, bilateral mammary hypoplasia occurred in two cases in which the pectoralis muscles appeared normal. Pterygium colli was a feature of Ullrich's (1930) atypical case.

Only a few cases exhibited functional anomalies which were probably congenital. Lachrymation was totally absent in Heubner's (1900) case ; this was also observed by Bernhardt (1894, 1897) in two cases with the analogous type of unilateral facial palsy. Sweat formation could not be stimulated on the face in the two siblings described by Köster (1920). The case of Kahlmeter (1916) presented several unusual features of uncertain nature, the chief of which were infantilism, vasomotor disturbances in the legs and a high sugar tolerance. Three cases were epileptic but none of them were regarded as mentally defective.

Mental defect.—In six cases there was clear evidence of subnormal mentality, four of these had reached adolescence or adult life and the other two were young children. The degree of amentia did not appear to be severe in any of these patients. A few other cases in infancy or early childhood were described as backward or possibly mentally defective. In assessing the mental state the retarding influence of the congenital palsies is apt to be misleading.

An analogous unilateral facial palsy.—A rarer type of congenital facial palsy is the unilateral variety which appears to be analogous to that under review. The palsy has the same distribution and characters as in the bilateral cases, but there is a greater tendency for it to be uncomplicated. Apart from abducens paralysis—which occurs in about half of the cases—cranial nerve palsies and structural defects of the limbs are infrequent. The abducens paralysis is usually bilateral, but occasionally only homolateral.

Amongst others, cases have been recorded by: Schultze (1892), Bernhardt (1894, 1897), Warrington (1897), Langdon (1899), Stéphan (1900), Minor (1900), Lagrange (1901), Comby (1901), Souques (1903), Babonneix and Miget (1932), Dupuy-Dutemps (1934) and Bálint (1936).

Pathology.

It is unfortunate that pathological evidence is available in only three of the published cases. They are those of Heubner (1900), Rainy and Fowler (1903) and Spatz and Ullrich (1931). The morbid anatomy and histology of these cases are of interest.

Heubner's case.—Male, aged 1 year and 7 months: died of bronchopneumonia. The chief clinical features were congenital facial diplegia,

bilateral abducens palsy and left lingual hemiparesis. The facial palsy had remained unchanged from birth, it was complete on the left side and of typical distribution on the right side, the muscles at the corner of the mouth being incompletely paralysed. There was no spasticity of the limbs. The more delicate functions of nervous control could not be tested on account of the age and mental retardation.

The complete neuromuscular units of the affected parts were not examined, only the brain and spinal cord being retained. Macroscopically, the medulla oblongata was asymmetrical, the left half being smaller than the right, and some of the tissue underlying the pyramid had a shrunken appearance. The right and left optic and oculomotor nerves and the left trochlear nerve looked normal, but neither the right trochlear nerve nor the abducens nerves could be found.

Histologically, the most notable abnormalities were seen in the motor nuclei of the cranial nerves, especially in the 6th, 7th and 12th, and to a lesser extent, in the 3rd and 11th. The 6th pair showed the most striking changes, ganglion cells being almost completely absent in both nuclei. In the 7th and 12th pairs the left-sided nuclei were the more abnormal, but the right also contained a diminished number of ganglion cells. Corresponding to the decrease in the number of cells the roots of the nerves were lacking or sparsely developed. The left accessory nuclei showed similar changes. The 4th nuclei were not specially mentioned, but the 5th, the 9th and the 10th were normal. The anomaly was not limited to the nuclei however. The medial longitudinal bundle was very hypoplastic on both sides, this corresponding in degree and extent with the affection of the nuclei. The formatio reticularis was sparsely developed, particularly on the left; the interstitial tissue was more affected than the nerve cells, but those nerve cells present were well developed. Both olives were hypoplastic, particularly the left, but the diminished number of nerve cells were normal in appearance. Further, on the left not only the fibres of the pyramidal tract streaming out from the motor nuclei appeared to be unusually sparse, but the whole pyramidal bundle, even in the lower part of the medulla, seemed to be under-developed. Marchi's stain failed to show any degenerative changes in the brain or cord.

Rainy and Fowler's case.—Female, aged 10 weeks: forceps delivery; died of broncho-pneumonia. The facial diplegia was almost complete, only slight contraction of a few medial fibres of the right frontalis muscle and drawing down of the right corner of the mouth being possible; there were no other nerve lesions and no structural anomalies. The whole neuromuscular unit of the 7th pair of nerves was examined. The brain and

nerves appeared normal, but there was gross "atrophy" of the facial muscles.

Serial sections from the 2nd cervical segment to a point above the 3rd nucleus were examined. The only abnormalities seen were in the 7th nerves and their nuclei. Both nerves showed marked degeneration, the ascending part of the root, the fasciculus teres and the emergent portion alike. "In the nuclei a large number of the cells ordinarily present had disappeared whilst those which remained presented a distinctly atrophic aspect, their processes being poorly developed, the Nissl's bodies irregular and the cells themselves much smaller than one would have expected. The apparently healthy cells of the 6th nuclei afforded a marked contrast to those of the 7th." Like the roots, the nerve trunks showed advanced degeneration. The few fragments of muscle which could be found were normal histologically.

Spatz and Ullrich's case.—Male, aged 3 months: died of bronchopneumonia. The facial diplegia was complete apart from drawing down of the left corner of the mouth, and there appeared to be complete ophthalmoplegia externa. Syndactyly was the only other anomaly.

The pons and medulla oblongata were relatively small, but the pyramids and olives were normal. The 3rd and 7th pairs of nerves were very thin and the 6th was absent, but the others appeared normal. No naked-eye changes were seen in the hemispheres or brain-stem on sectioning.

Histological changes were seen in the 3rd, 4th, 6th and 7th nuclei. The 6th were the most severely affected, the nuclei were unduly small, but of normal appearance, and the roots were also small. The 4th nuclei were not in the usual place but were represented by scattered elements lateral to it; the root fibre bundles were very small. The nerve cells in the 3rd nuclei were reduced in number and the roots were correspondingly small.

Bálint's case.—Bálint (1936) reported the autopsy findings in an infant 3 months old with congenital 6th and 7th nerve palsy on the left side. The facial palsy was atypical, being incomplete in the frontalis and orbicularis oculi and the triangularis and mentalis muscles. Twitchings of the facial muscles were observed.

Histological examination revealed a degenerative process which involved both abducens nuclei, the left being almost completely destroyed and the right considerably damaged. The fasciculus teres of the left facial nerve was also disorganized, with secondary degeneration of the nucleus. No further details are given in the report.

Comment.—The similarity of the pathology in the cases of Heubner and

of Spatz and Ullrich strongly supports the view that nuclear hypoplasia accounts for the cranial nerve palsies in all typical cases of the syndrome. Heubner's case with extensive nuclear lesions shows that a more diffuse hypoplasia of nervous elements may also occur. The degenerative changes in the 7th nerves and nuclei in Rainy and Fowler's atypical case of uncomplicated facial diplegia may have been due to forceps trauma of the facial nerves as suggested by Zappert (1910). It would seem reasonable to suppose that the pathology of some of the cases without multiple cranial nerve involvement or structural defects may also be of a similar nature. However, the fact that the distribution of the facial palsy usually corresponds with that of the more typical cases of the syndrome supports the view that it probably has a similar origin in most of these cases. An intra-partum hæmorrhage in the medulla appeared to be responsible for the unilateral 6th and 7th palsy in Bálint's case. I have referred to this case because it suggests that a similar pathology may be not infrequent in the apparently analogous group with unilateral facial palsy.

In the congenital eye muscle palsies absence or hypoplasia of the muscles concerned has frequently been observed at operation, but this may sometimes be secondary to nuclear aplasia. Destructive processes which involve the nuclei are sometimes the cause of the palsy as in Bálint's case. It is probable, however, that nuclear aplasia is the usual cause of bilateral congenital ocular palsies as in a case recently demonstrated by Phillips, Dirion and Graves (1932). In a 5-year-old child with an uncomplicated congenital bilateral abducens palsy they found an hypoplasia of the 6th pair of nuclei and nerves.

Historical Review.

The writings of Moebius (1888, 1892) on the subject of "Infantiler Kernschwund" attracted considerable attention and excited a good deal of controversy. He regarded congenital cranial nerve palsies and those acquired in infancy and early childhood as fundamentally the same. He classified the forty-three cases of cranial nerve palsy in young children, which he reviewed, into six groups. Combined 6th and 7th nerve palsy comprised one of these groups. He found six examples in the literature—the first five of this series and the case described by Recken (1891) which was acquired. Moebius thought that 6th and 7th nerve palsies probably could not occur independently on account of the close relationship of their nuclei. In the absence of pathological evidence he thought the condition was most likely a degenerative one involving the nuclei of the affected nerves and that it was probably toxic in origin.

The views of Moebius were, for the most part, generally accepted, although several earlier writers were nearer the mark than he. Chisolm (1882) thought the lesion in the third case of this series was "a local aplasia of the grey matter in the medulla." Mauthner (1885) and Hirschberg (1887) thought that an aplasia of the cranial nerve nuclei accounted for these congenital palsies.

A change of opinion in favour of the aplastic conception followed the admirable review by Kunn (1895) of the subject of congenital ocular palsy in which he sharply differentiated between congenital and acquired types, and considered the former to be due to an aplasia of the corresponding nuclear cells. This hypothesis appeared to be confirmed by the pathological evidence of Heubner's typical case in 1900. The contradictory evidence presented by Rainy and Fowler's atypical case a few years later tended to confuse the issue, but the agenetic view continued to prevail pending further evidence. This was long denied, and not until 1931, when Spatz and Ullrich's case with multiple palsies was described, was confirmation of Heubner's findings realized.

Alajouanine, Huc and Gopcevitch (1930) thought they were the first to describe the association of club-foot with congenital facial diplegia, whereas nine of the cases of the present series previously recorded exhibited this anomaly.

Thomas (1898), Cabannes (1900) and Falloux (1909) reviewed the reported cases of congenital facial palsy, although they failed to include several of the hitherto published cases. More recently, brief and incomplete reviews were published by Fry and Kasak (1919), Kirby (1923) and Bonar and Owens (1929). Neurath (1907) and Zappert (1910) reviewed the available pathological evidence regarding congenital cranial nerve palsies in general, but the cases were few and varied and their conclusions were indefinite.

Ætiological Considerations.

Hereditary factors.—Although males predominated, there was no significant difference in the sex incidence. Out of fifty-seven cases in which it was stated, thirty-four were males and twenty-three were females.

In four instances two or more members of a family were affected. Thomas's (1898) two cases were brothers, as were Köster's (1902), while a sibling of one of Cadwalader's (1922) cases was said to have been similarly affected. The three cases described by Beetz (1913) were siblings, and a fourth child of this ill-fated family, who died aged 15 months, was said to have had a mask-like face from birth and almost certainly suffered from the same congenital anomaly. There was a family history of congenital

defects in Thomas's cases, also in Lennon's (1910) elder case and that of Fry and Kasak (1919). Though a family history of congenital deformities is not mentioned in any of the other cases it is probable that this may not always have been a matter of careful inquiry.

It is of interest to note that the siblings of Thomas, Köster and Cadwalader all belonged to the small group of uncomplicated facial diplegia. Consanguinity was a feature of the family described by Beetz in which there had been two instances of intermarriage in the previous three generations ; the family lived in an isolated valley of the Black Forest where intermarriage is notoriously frequent. It is well to recall here that none of the three cases of this family was typically affected. It is evident that there is a definite tendency for the condition to show a familial incidence.

Ptosis is the commonest type of congenital eye muscle palsy: it usually has strong hereditary characters, the dominant being more frequent than the recessive type. Only occasionally can an hereditary factor be traced in the other types of congenital ocular palsy, such as those encountered in the syndrome under review. The hereditary type of ophthalmoplegia externa is rarely congenital: it usually exhibits dominant characters and makes its appearance in adolescence or later.

Toxic, vascular and mechanical theories.—Syphilis is no longer suspect in this condition ; serological evidence was negative in each of the eight cases in which it was sought. Alcohol and other toxic agents were incriminated by some authors. Others thought that vascular defects might be the cause of the nuclear agenesis, but their views were purely hypothetical.

Mechanical influences of an extraneous nature were frequently exploited in this as in many other congenital anomalies. Some thought that pressure on the brain, arising from disturbances in its immediate surroundings, might explain the nervous phenomena.

Ullrich's hypothesis.—Ullrich (1930, 1936), who has been speculating on the ætiology of this syndrome for a number of years, believes that he has at last found a satisfactory explanation which accounts for its diverse features. His hypothesis is based on the embryological studies of Kristine Bonnevie (1934) who claims to have shown how somewhat similar anomalies arise in an experimental strain of mice. The mice belonged to the strain raised by Bagg and Little (1924, 1929) in the United States. They exhibited congenital deformities of the limbs and eyes in a high percentage of cases. These mutations were initiated by means of X-rays and their incidence was augmented by in-breeding through many generations: recessive genes were responsible for their passage.

In an endeavour to discover how the anomalies arise Bonnevie examined seven hundred live embryos of the Bagg-Little tribe at various stages of development. She claims to have shown that the fundamental error, which gives rise to all the anomalies, is an excessive production of cerebrospinal fluid by the newly-formed choroid plexuses of the developing brain. After the embryos attained a length of 7 mm. small subcuticular vesicles appeared on the back of the neck. In larger embryos increasing intra-vesicular tension appeared to be responsible for the dissipation of the contained fluid in the directions of least resistance, the elasticity of the cuticle being the displacing force and the least resistance being encountered on the most concave parts of the surface. The fluid finally came to rest in the orbital regions and at the ends of the limbs, but no permanent damage was done until it reached these situations. The pressure of the stationary fluid on the delicate underlying tissues usually caused capillary damage with intra-vesicular hæmorrhage and hæmatoma formation: thrombosis occurred in the subjacent vessels.

Comment.—Although no more than suggestive, Ullrich's hypothesis is the only one which would appear to have any justification. A critical examination of this new theory thus becomes necessary. No one has confirmed Bonnevie's observations. Plagens (1933) attempted to do so and failed, but he was not working with live embryos. However, Bonnevie's observations cannot be regarded with indifference, both because of their uniformity and of the high scientific reputation of the author. It is interesting to inquire how the cerebrospinal fluid could reach the subcutis to form the primary vesicle as postulated by Bonnevie. The fascinating experiments of Weed (1917) on the establishment of the cerebrospinal circulation show that an initial excess of cerebrospinal fluid would, in fact, be likely to take such a course.

Assuming that Bonnevie's explanation of the deformities in the Bagg-Little mice is the correct one, is there any justification for assuming that a similar process might account for the anomalies of the congenital syndrome under review? Ullrich finds no difficulty in applying it to these cases, but there are certain fallacies which appear to render his analogy untenable. He supposes that the primary vesicle overlying the roof of the 4th ventricle would press the roof against the floor of the ventricle and thus inhibit the development of the motor nuclei in that situation. This would, of course, be impossible owing to the greater intra-ventricular pressure which causes the fluid to filter through the temporary superior membranous area in the roof of the 4th ventricle. Further, if the pressure of the intra-ventricular fluid were sufficiently raised to damage the adjacent

ectodermal tissue it would be most unlikely to exert a selective effect on certain nuclei to the exclusion of others.

For the purpose of testing Ullrich's hypothesis I intended to examine the brain-stems of a series of Bagg-Little mice for nuclear defects, but I was unable to procure them. If Ullrich's views are correct one would have expected to find evidence of hypoplastic motor nuclei.

It would appear then, that although such a process as described by Bonnevie might conceivably account for the limb and pectoralis muscle defects in the patients of this syndrome, it could not possibly be the cause of the nuclear defects in the brain. As all the anomalies are most likely to be due to a common factor one must conclude that Ullrich's hypothesis is untenable and that the ætiology of this congenital syndrome is still obscure. Bonnevie, Plagens and others agree that thrombosis, however it may arise, is a potent cause of congenital defects in experimental animals. Perhaps it accounts not only for the deformities of this syndrome, but also for the cerebral hypoplasia.

Summary.

A review of the literature on the subject of congenital facial diplegia has been undertaken. A well-defined clinical picture has emerged as a result of this study.

A typical case has been described in detail, the patient being a girl aged 3 years.

The facial diplegia was usually accompanied by other cranial nerve palsies, while malformations of the limbs were frequently encountered The incidence of the principal anomalies was as follows:—

Facial diplegia	61 cases
Abducens palsy	45 „
Ophthalmoplegia externa	15 „
Ptosis	6 „
Lingual palsy	18 „
Mental defect	6 „
Club-foot	19 „
Brachial malformation	13 „
Pectoralis muscle defect	8 „

The facial diplegia was complete in one-third of the cases. When the palsy was incomplete the distribution was characteristic, the peri-oral muscles being least affected and usually the only ones capable of any movement. No other type of facial palsy has such a distribution.

Pathological data are available in only three cases. The basis of the cranial nerve palsies was an aplasia or hypoplasia of the relevant nuclei and the nerves and muscles connected therewith.

The ætiology of congenital facial diplegia is obscure. The principal theories regarding it have been discussed.

It is a pleasure to acknowledge my indebtedness to Professor Charles McNeil for the interest he has shown in this work.

REFERENCES.

ABRAHAMSON, I. (1921), *Arch. Neurol. Psychiat.*, **5**, 621.
ALAJOUANINE, T., HUC, G., and GOPCEVITCH, M. (1930), *Rev. neurol.*, **37**, ii, 501.
ALLEN, I. M. (1931), *Proc. R. Soc. Med.*, **25**, i, 45.
BABONNEIX, L., and MIGET, A. (1932), *Gaz. Hôp.* Paris, **105**, 941.
BACH, L. (1893), *Zbl. Nervenheilk.*, **16**, 57.
BAGG, H. J. (1929), *Amer. J. Anat.*, **43**, 167.
BÁLINT, A. (1936), *Jb. Kinderheilk.*, **147**, 256.
BATTEN, F. E. (1905), *Brain*, **28**, 359.
BEETZ, P. (1913), *J. Psychiat. Neurol.*, **20**, 137.
BERNHARDT, M. (1894), *Neurol. Zbl.*, **13**, 2.
——(1897), *Ibid.*, **16**, 296.
——(1901), "Festschrift fur Max Jaffe," Braunschweig, p. 34.
BIELSCHOWSKY, A. (1932), "Handbuch der Augenheilkunde," Graefe-Saemisch, "Die Lahmungen der Augenmuskeln," Berlin, 2 Aufl., 380.
BLOCH, P. (1891), Thesis, Berlin. Cited by Thomas.
BONAR, B. E., and OWENS, R. W. (1929), *Amer. J. Dis. Child.*, **38**, 1256.
BONNEVIE, K. (1934), *J. exp. Zool.*, **67**, 443.
CABANNES, C. (1900), *Rev. neurol.*, **8**, 1011.
CADWALADER, W. B. (1922), *Amer. J. med. Sci.*, **163**, 744.
CAMERON, H. C. (1924), *Proc. R. Soc. Med.*, **17**, viii, 28.
CHISOLM, J. J. (1882), *Arch. Ophthal.* New York, **11**, 323.
COLLINS, E. T. (1909), *Zbl. prkt. Augenheilk.*, p. 208, Cited by Wilbrand u. Saenger.
——(1915), *Trans. ophthal. Soc. U.K.*, **35**, 371.
COMBY, J. (1901), *Arch. Méd. Enf.*, **4**, 742.
DECOURT, J., and PERREAU, P. (1935), *Ibid.*, **38**, 419.
DECROLY, O. (1902), *J. Neurol.*, **7**, 474.
DUPUY-DUTEMPS, L. (1934), *Bull. Soc. Ophtal. Paris*, vi, 365.
ERRECART, P. L. (1930), *Rev. Espec. Asoc. med. argent.*, **5**, 930.
FALLOUX, C. (1909), *Thèse de Paris.*
FRY, F. R. (1920), *J. Amer. med. Ass.*, **74**, 1699.
——and KASAK, M. (1919), *Arch. Neurol. Psychiat.*, **2**, 638.
FRYER, B. E. (1892), *Ann. Ophthal. Otol.*, Kansas City, **1**, 82. Cited by Thomas.
GAREISO, A., and BARBIERI, C. A. (1933), *Prensa méd. argent.*, **20**, 1713.
GARRAHAN, J. P., and CUCULLU, A. (1932), *Sem. méd.*, Buenos Aires, **1**, 592.
VAN GELDER, A. H., and WEYL, S. (1927), *Med. Tijdschr. Geneesk*, ii, 2344.
GIERLICH, N. (1905), *Dtsch. med. Wschr.*, **31**, 1462.
v. GRAEFE, A. (1880), "Graefe-Saemisch Handbuch." Leipzig, 1 Aufl., **6**, ii, 60.
GÜTERMANN, F. (1917), *Dtsch. Z. Nervenheilk.*, **57**, 203.
GÜTZMANN, H. (1905), *Dtsch. med. Wschr.*, **31**, 2033.
HARLAN, G. C. (1881), *Trans. Amer. ophthal. Soc.*, **3**, 216. Cited by Moebius.
HEUBNER, O. (1900), *Charité-Ann.*, **25**, 211.

HIRSCHBERG, J. (1887), "Wörterbuch der Augenheilkunde." Leipzig, p. 86. Cited by Zappert.
KAHLMETER, G. (1916), *Hygiea.* Stockholm, **78**, 1321.
KIRBY, D. B. (1923), *Arch. Ophthal.* New York, **52**, 452.
KIRMISSON, E. (1895), *Rev. Orthop.*, 1re Série, **6**, 9.
KUNN, C. (1895), *Deutschmann's Beitrage zur Augenheilkunde*, Heft 19, 1.
LAGRANGE, F. (1901), *Soc. franç. Ophtal.*, Mai. Cited by Cabannes.
LANGDON, F. W. (1899), *J. nerv. ment. Dis.*, **26**, 593.
LENNON, M. B. (1910), *Calif. State J. Med.*, **8**, 115.
LITTLE, C. C., and BAGG, H. J. (1924), *J. exp. Zool.*, **41**, 45.
MANDELS, S. (1928), *Russk. oftalm. Z.*, **8**, 84. Cited in *Zbl. ges. Ophthal.*, 1928, **20**, 745.
MAUTHNER, L. (1885), "Die Nicht Nuclearen Lahmungen der Augenmuskel," p. 432. Cited by Recken.
MINOR, L. S. (1897), *Arch. Neurol.*, **2**, 354.
MOEBIUS, P. J. (1888), *Münch. med. Wschr.*, **35**, 91.
——(1892), *Ibid.*, **39**, 17, 41, 55.
NEURATH, R. (1907), *Ibid.*, **54**, 1224.
PERITZ, G. (1912), "Die Nervenkrankheiten des Kindesalters." Berlin, p. 140.
v. PFAUNDLER, M. (1913). Cited by Ullrich (1936).
PHILLIPS, W. H., DIRION, J. K., and GRAVES, G. O. (1932), *Arch. Ophthal.* New York, **8**, 355.
PLAGENS, G. M. (1933), *J. Morph.*, **55**, 151.
PROCOPOVICI, E. (1896), *Arch. Augenheilk.*, **34**, 34. Cited by Thomas.
RAINY, H., and FOWLER, J. S. (1903), *Rev. Neurol. Psychiat.*, **1**, 149.
RECKEN, — (1891), *Klin. Zbl. Augenheilk.*, **29**, 340.
SCHAPRINGER, A. (1889), *Boston med. surg. J.*, p. 635.
SCHMIDT, A. (1897), *Dtsch. Z. Nervenheilk.*, **10**, 400.
SCHULTZE, F. (1892), *Neurol. Zbl.*, **11**, 425.
SNOWBALL, T. (1915), *v. Graefe's Arch. Ophthal.*, **90**, 155.
SOUQUES, A. (1903), *Gaz. Hôp.* Paris, **76**, 132.
SPATZ, H., and ULLRICH, O. (1931), *Z. Kinderheilk.*, **51**, 579.
STÉPHAN, B. H. (1888), *Med. Tijdschr. Geneesk.*, 2.R., **24**, 113.
TAYLOR, S. (1902), *Trans. clin. Soc. Lond.*, **35**, 177.
THOMAS, H. M. (1898), *J. nerv. ment. Dis.*, **25**, 571.
ULLRICH, O. (1930), *Z. Kinderheilk.*, **49**, 271.
——(1936), "Handbuch der Neurologie," Bumke u. Foerster. Berlin, 1936, **16**, 139.
WARRINGTON, W. B. (1897), *Ophthal. Rev.*, **16**, 99. Cited by Wilbrand u. Saenger.
WEED, L. H. (1917), "Contributions to Embryology," Publ. Carneg. Instn. No. 225, Vol. 5, No. 14.
WELDE, E. (1912), *Charité-Ann.*, **36**, 124.
WILBRAND UND SAENGER (1921), "Neurologie des Auges," München u. Wiesbaden, **8**, 179.
YEALLAND, L. R. (1931), *Proc. R. Soc. Med.*, **24**, 1066.
ZAPPERT, J. (1910), *Ergebn. inn. Med. Kinderheilk.*, **5**, 305.
ZIEHEN, T. (1908), *Berl. klin. Wschr.*, p. 1557.

DYNAMICS OF HOMONYMOUS HEMIANOPIAS AND PRESERVATION OF CENTRAL VISION.

BY M. B. BENDER AND M. G. KANZER

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An analysis of homonymous hemianopias associated with tumours of the brain reveals a considerable percentage of cases in which there is preservation of the central field, the so-called "macula-sparing" hemianopias. In a study of 600 cases of brain tumours, complete or "macula-splitting" hemianopias were uncommon in tumours of the suprageniculate pathways.

In our series of cases, it was found that the periphery of the field of vision was affected first, the hemianopias progressing towards the centre. In the cases of brain tumour and hemianopia reported in the literature, the earliest defects in the homonymous fields were invariably in the periphery (Cushing, 1921; Globus and Silverstone, 1935; Bender and Strauss, 1937). Associated with these changes in panoramic vision for black and white were disturbances in colour vision. The hemianopias for colour invariably preceded those for black and white, and again the disturbances progressed from the periphery to the macula. It seemed that the various field defects recorded in our series of cases were stages in the development of the hemianopia, and in all these instances, vision in the macular region was last to disappear.

The zone of preserved central vision in the cases studied ranged in extent from 5° to 30° from the fixation point depending on the degree of acuity and the extent of the hemianopia.[1] This preservation of central or "macular" vision occurred irrespective of which part of the optic radiation was involved by the tumour. Moreover, it was noted that the character and the development of the hemianopia were similar in neoplasms of the temporal and occipital lobes. In almost all instances, the homonymous field of vision contracted from the periphery centrally.

[1] The actual extent of the area of macular vision is from 2° to 10° around the fixation point.

I.—Stages of Hemianopias.

The following case reports illustrate various stages in the development of homonymous hemianopias. There were many such examples but space does not permit their full description.

Case 1.—A 42-year-old male was first admitted to the hospital in July, 1936, with a history of severe headaches which began suddenly while straining at stool. The onset was accompanied by vertigo and vomiting. Previously the patient had been subject to milder headaches for four months. Examination on admission revealed nuchal rigidity and bilateral Kernig sign. There was marked mental confusion and aphasic symptoms. Visual field defects were noted but could not be plotted. Lumbar puncture yielded deeply bloodstained fluid. The patient improved and was discharged with a diagnosis of subarachnoid hæmorrhage.

In December, 1936, he had a generalized convulsion and persistent headache,

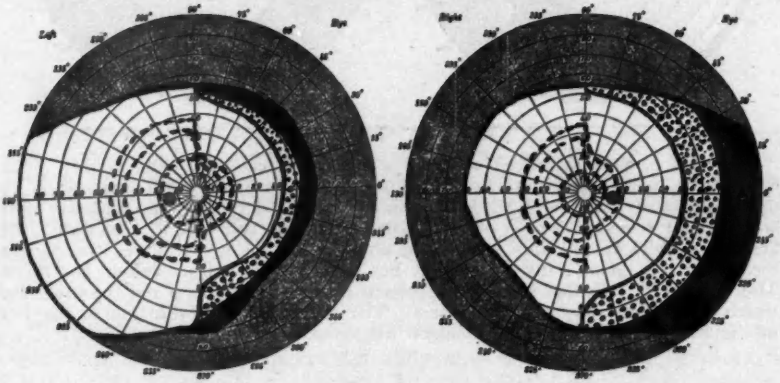

Fig. 1.—Early right homonymous hemianopia. The solid area represents an absolute scotoma for 10 mm. test object. The stippled area is a relative scotoma for 4 mm. test object. Dashes indicate colour vision as determined by 10, 4 and 2 mm. test objects.

drowsiness and mental symptoms. Examination on the second admission revealed an incomplete right homonymous hemianopia (fig. 1) and symptoms of mixed aphasia. An encephalogram revealed internal hydrocephalus. The symptoms persisted. A craniotomy was performed and a cyst was discovered in the left temporo-parietal region. Needle aspiration yielded 2 c.c. of yellow fluid. After operation the condition of the patient was unchanged except for increased aphasic difficulties.

Comment.—This is an example of an early peripheral defect in the homonymous fields of vision.

Case 2.—A 47-year-old housewife entered the hospital because of frontal headache, blurred vision, and speech difficulty of four weeks' duration.

Examination disclosed a slight right facial weakness, anosmia and blurring of the optic discs. Perimetric field examinations showed an incomplete right homonymous hemianopia. When she was asked to bisect horizontal lines she invariably

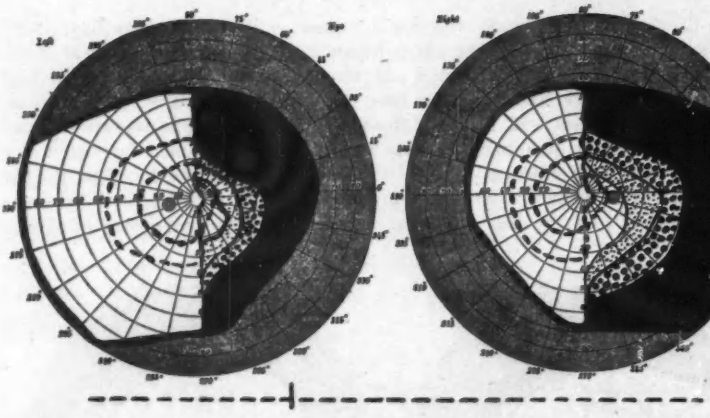

FIG. 2.—A more advanced stage of a right homonymous hemianopia. Such field defects were not uncommon. The hemianopia is incongruent and greater in the upper quadrant. Solid black represents outer border for 10 mm.; heavy dots is border for 4 mm. and light dots is border for 2 mm. test object. The dash lines are colour fields for 10 and 4 mm. test objects. In the stippled area the patient recognizes motion of a 10 mm. object but can perceive neither colour nor form. The horizontal dash line below the perimetric fields represents a red coloured line which the patient was asked to bisect. The patient divided the line to the left of the true midpoint, but soon realized her error.

divided the line to the left of the true midpoint. Once she realized her error and remarked that she did not notice the right side (fig. 2).

A ventriculogram confirmed the clinical diagnosis of left temporal lobe tumour. At operation a neoplasm was located deep in the left temporal lobe.

Comment.—This is a more advanced stage of a homonymous hemianopia. An interesting feature was the patient's division of the horizontal line to the left of the actual midpoint. Apparently the patient formed a new macula. The formation of a pseudo-fovea is not uncommon in individuals with homonymous hemianopia.

Case 3.—A 17-year-old boy was admitted with a history of illness of five weeks' duration. The symptoms included weakness of the left upper and lower extremities, difficulty in swallowing with nasal regurgitation and spells of dizziness associated

with unpleasant olfactory sensations. Examination revealed incomplete left homonymous hemianopia (fig. 3). An exploratory craniotomy was performed and tumour tissue removed from the region of the right posterior temporal lobe. The extent of the tumour could not be determined. The post-operative recovery was uneventful. Histological studies of the tumour revealed a neurospongioblastoma.

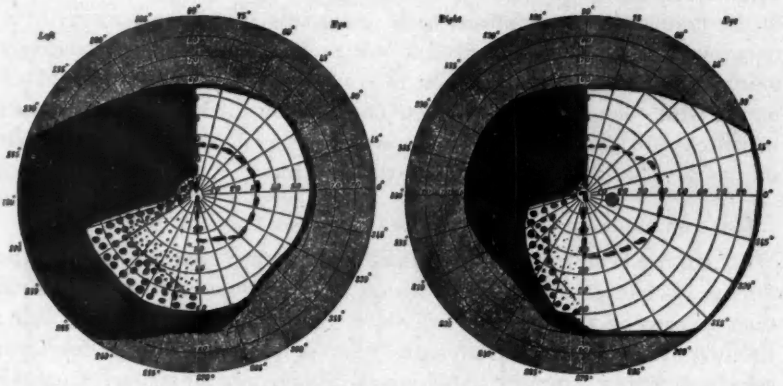

FIG. 3.—Incomplete left homonymous hemianopia with the defect, except for central vision, being greatest in the upper quadrants. The solid black is an absolute scotoma. The heavy dots indicate recognition of motion by a 10 mm. object. The small dots represent the same function for a 4 mm. object. More centrally, objects appeared clearer. The dash lines represent the visual field determined by a 4 mm. green test object, showing a macula-splitting hemianopia for colour.

Comment.—In the inferior left homonymous quadrants the vision was contracted from the periphery centrally and the acuity was very much reduced. The defect was greatest in the periphery and least in the centre. The colour hemianopia was complete, there being no sparing of the macular region. Apparently the fibres conducting light impulses from the right homonymous upper retinæ were not entirely destroyed although definitely damaged. The function of the rest of the right optic radiation was completely impaired. This is an example of a more advanced stage of homonymous hemianopia. If the disease process were permitted to continue without operative interference the hemianopia would become complete. The defects in the fields of vision show incongruity; the nasal half was more extensively affected than the temporal. This was a common finding.

The foregoing data show that the development of a hemianopia is progressive in character. Examination limited to a single perimetric determination discloses field defects which are only phases in the development

of the hemianopia. When subsequent field examinations are made at later stages of the process, the extent of visual impairment is often found to have increased. This was demonstrated in several of a series of cases reported by Bender and Strauss (1936). In the early stages, there may be a peripheral temporal crescentic scotoma ; later, a defect may be discovered in the homonymous peripheral field ; eventually, when the homonymous paracentral zone becomes affected, the central region is still relatively uninvolved. Careful examination of this supposedly spared " macular " region with coloured and small test objects may disclose a colour defect which extends up to the fixation point. Such studies tend to reveal that the hemianopia for colour precedes that for form.

II.—The Loss of Colour Vision Preceding Loss of Form Vision.

There has been frequent confirmation of the fact that in lesions of the supragenículate pathways, colour vision is usually more severely impaired than is perception of black and white (Magitot and Hartmann, 1926 ; Brouwer, 1936). It is not unusual to find a quadrantic defect for form associated with a complete homonymous hemianopia for colour. Our own observations also show that in the progressive development of hemianopia, colour vision is affected first and that at a time when testing with form objects shows " macula-sparing," tests with red, blue or green objects will already show a complete macula-splitting hemianopia. In these cases the central area of vision is only relatively preserved and there are definite indications that macular fibres are involved.

The conduction of colour vision has been regarded by some authors as separate from the conduction of black-white sensation. In support of this supposition, cases of " pure " colour hemianopia have been cited. Wechsler (1933) gives an excellent review of the literature upon the subject of dissociation of colour and form vision. In two cases in which post-mortem examination was performed by Lenz (1921), lesions were found in the occipital radiation. Brouwer (1936) points out that the assumption of separate conduction of colour vision is unnecessary and it is probable that in most cases of colour hemianopia, careful examination will reveal that black-white vision is not completely unaffected. We followed his suggestion but detailed perimetric testing in patients with colour hemianopia showed no change in black and white perception. The following are examples.

Case 4.—The patient was a 23-year-old female who was admitted with a history of headache, nausea and convulsions of four weeks' duration. She also had visual hallucinations of formed images and figures. A physician detected a suggested left homonymous hemianopia on one occasion. Lumbar puncture showed 200 red

blood-cells in the spinal fluid. Neurological examination revealed bilateral papillœdema, symptoms of meningeal involvement and a left homonymous visual defect for colour but not for form. The diagnosis was subarachnoid hæmorrhage.

In the hospital, the condition of the patient improved rapidly. Repeated visual field examinations showed gradual improvement in the perception of colour. Perimetry executed three years later showed an incomplete left homonymous hemianopia for colour which was most evident for 1 mm. green test object. There was absolutely no disturbance in the peripheral fields of vision for black and white (fig. 4).

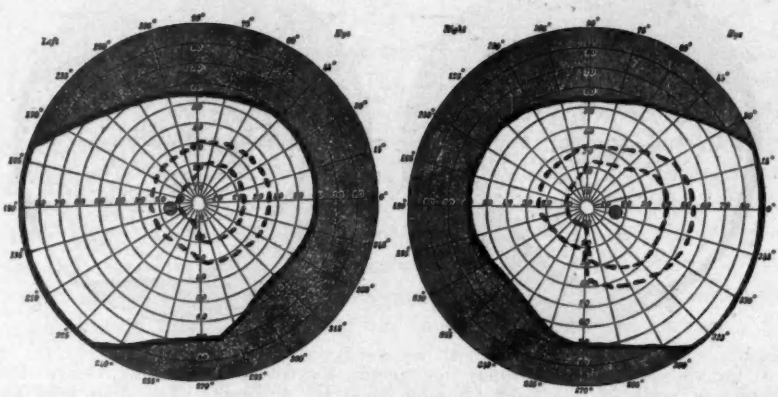

FIG. 4.—Left incomplete homonymous hemianopia for colour. Dash lines represent the fields as established with 10 and 4 mm. coloured test objects. The outer form field was determined with 10, 4 and 2 mm. objects. This revealed no defects.

Comment.—These observations are at variance with Brouwer's hypothesis. It is possible that some of the fibres scattered throughout the optic radiation were damaged at a focal point and this resulted in a partial reduction in the visual acuity which became manifest in the form of a hemianopia for colour.

Case 5.—A 36-year-old female was admitted following an attack in which she lost consciousness but was not convulsed. There was a history of a craniotomy at another hospital six months previously. At that time, a large tumour of the gasserian ganglion was reported to have been completely removed. Before the operation there had been weakness of the left extremities which had partially recovered their power since the removal of the tumour. After the operation she suffered from attacks of depression, absent-mindedness and difficulty in spelling and speech. Examination at the time of admission showed a right homonymous visual field defect for colour (fig. 5). Except in the "macular area" she was unable

to recognize colour, form, or objects in the right homonymous field of vision. She was, however, able to appreciate movement even in the most extreme periphery of the defective right field of vision.

No other noteworthy symptoms developed and the patient was discharged. She was examined periodically during this time. Repeated perimetry disclosed loss of recognition of form and colour but retention of appreciation of movement in the right homonymous fields.

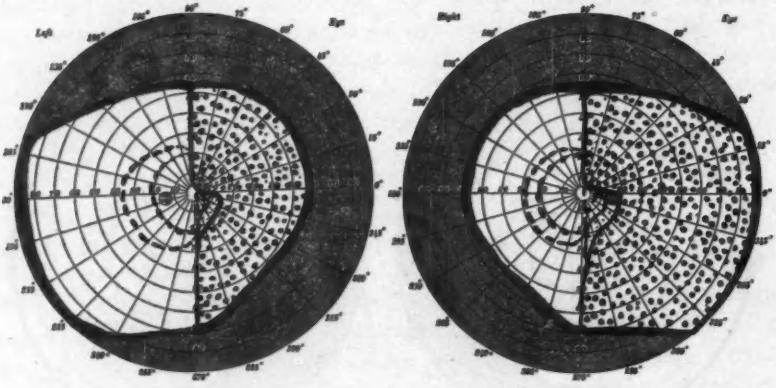

FIG. 5.—Right homonymous hemianopia for colour and form. Heavy dots represent areas in which only motion could be perceived. The dash lines are outlines of colour fields for 4 and 2 mm. objects and show a macula-splitting hemianopia. There is no absolute scotoma in the peripheral fields.

Comment.—This is an example of homonymous hemianopia for recognition of form and colour and preservation of recognition of movement even at the most extreme periphery of the field of vision. We lack an explanation for this observation even though there may be many hypotheses.

Whichever hypothesis be correct, it appears that the early loss of colour vision is a sign of impairment of the finer functions of the optic pathways. Since visual acuity as well as colour vision is progressively impaired as the optic radiation is gradually involved, it is evident that the peripheral defects are only part of a greater disturbance in vision. If the anatomical facts be considered, it is clear that where an infiltrating lesion, such as a tumour, affects the optic radiation by œdema, the function of the entire radiation, including the peripheral and central fibres, will be disturbed. Since the peripheral fibres are fewer in number and occupy a smaller area than the central fibres, and inasmuch as they represent areas of less visual

acuity,[1] their functional impairment is more readily followed by visual field defects. Consequently the earliest defect in the field of vision makes its appearance in the periphery. In the more central parts of the field of vision, the earliest sign of partial impairment of the functions of the central optic fibres is found to be the loss of acuity for colour vision. Only after the functional impairment has become severe is the acuity for black-white perception affected. This, of course, depends on the number of conducting fibres destroyed.

III.—Macular Vision and Occipital Lobe Tumours.

The foregoing data show that central vision for form is often preserved in homonymous hemianopias. The occurrence of homonymous hemianopias with "sparing of macular vision," in these cases, has led some observers to postulate bilateral cortical representation of each macula. Foerster (1929) and Penfield, Evans and MacMillan (1935) believed that sparing of macular vision after removal of the occipital lobe afforded evidence of bilateral representation of the macula. These observations were used to support the theory that macular fibres decussate through the corpus callosum to reach the opposite occipital lobe. Pfeiffer (1925) found such a decussation, but Putnam (1926) was unable to confirm this finding.

The preservation of central vision in a homonymous hemianopia resulting from an occipital lobe tumour may be explained by any one of several theories. A hypothesis of bilateral cortical representation has many adherents but at variance with it are certain facts: (1) Numerous anatomical studies made on experimental animals showed that the two suprageniculate pathways are not connected through the corpus callosum or by other association fibres (Poliak, 1932). (2) Clinico-pathological observations revealed that lesions of one occipital pole produced contralateral homonymous hemianopic central field defects (Holmes and Lister, 1916; Holmes, 1918; Wilbrand, 1907), and that tumours of the occipital lobe may produce macula-splitting hemianopias. The available data seem to indicate that the homonymous half-maculæ are represented in one occipital lobe. Support for the theory of bicortical macular representation, however, is found in clinical observations of preserved central vision in patients with occipital lobe tumours (Allen, 1930; Horrax and Putnam, 1932). Thus, the tumours in some of our cases invaded the cortical macula in the occipital

[1] Functionally, it has been shown by Traquair (1938) that the acuity in a highly illuminated field of vision is greatest in the centre and decreases toward the periphery. The threshold visual stimulus for the central area is less than for the peripheral field of vision. This is also true for colour vision.

lobe, leaving only a small portion, the most anterior part, intact (Case 6). In other instances, the tumour did not involve the calcarine cortex but was localized on the lateral aspect of the occipital lobe (Case 7).

Case 6.—A 32-year-old male was admitted to the hospital with a history of generalized convulsive seizures during the past eight years. These attacks had become increasingly frequent, and recently headaches and impairment of memory had developed. The examination revealed signs of a lesion in the left

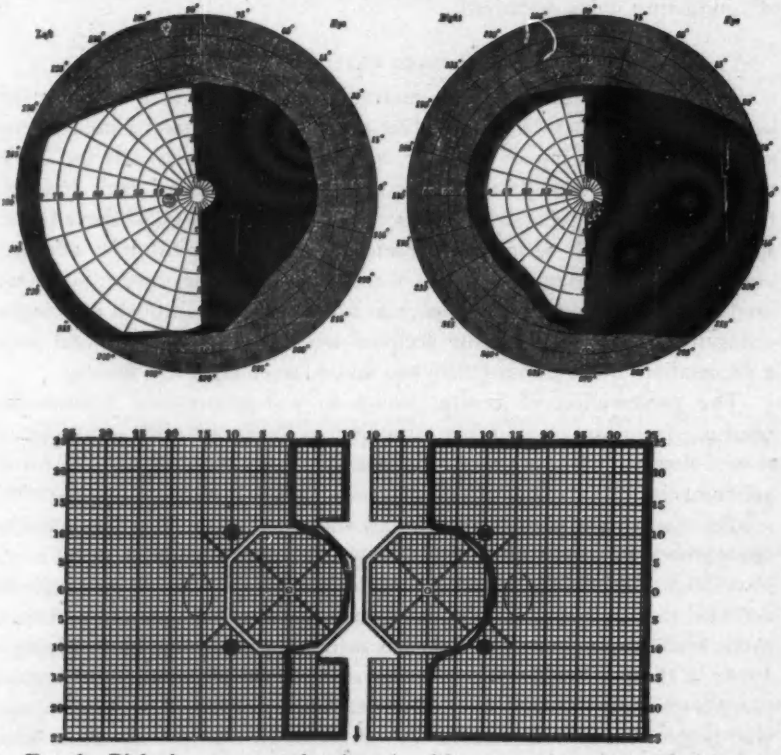

FIG. 6.—Right homonymous hemianopia with preservation of central vision. The lower chart is plotted from a stereocampimeter.

cerebral hemisphere, including a right homonymous hemianopia with sparing of central vision. A craniotomy was performed and some calcified tumour tissue was removed from the occipital pole. Histological study of the excised brain tissue suggested a vascular anomaly. Perimetry now disclosed the right homonymous hemianopia to be more complete. There was an area of apparent central vision remaining, being 5° to 10° from the fixation point. Stereocampimetry showed an area of preserved central vision (fig. 6).

The convulsive seizures continued and a second operation after a lapse of eight months revealed cystic changes in the occipital lobe, which was amputated behind the temporo-parietal junction. Following the second operation, examination of the fields of vision revealed a right homonymous hemianopia which seemed to spare the macula from 2° to 5°. On the tangent screen test and on stereocampimetry the zone of apparently preserved vision was not circular in its outline. The inner border of the hemianopia was an irregular wavy vertical meridian (fig. 7). This was due to formation of a new macula.

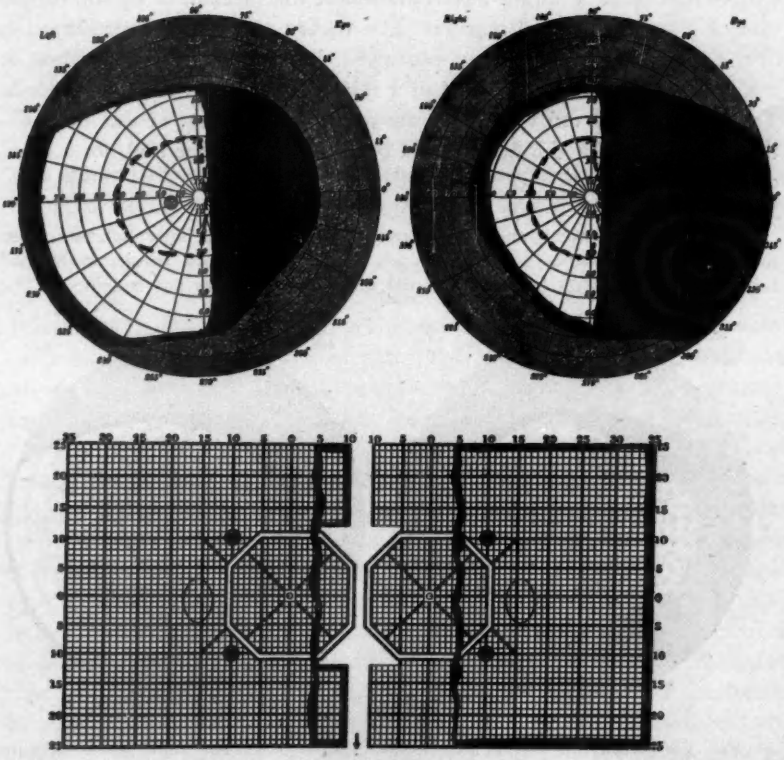

FIG. 7.—The same patient after ablation of the left occipital lobe: Right homonymous macula-splitting hemianopia with formation of a new central fixation point. This caused the hemianopia to be shifted 5° to the right of the new fovea.

Four years later a perimetric examination disclosed a right homonymous hemianopia and the formation of a new macula. The macula-splitting hemianopia was 3° to 5° to the right of the point which the patient was asked to fix during perimetry.

Comment.—This is an example in which the lesion involved the cortical macula and yet the macular field of vision seemed to be preserved. Amputation of the occipital pole did not abolish macular vision. Only after the entire occipital lobe was excised did the hemianopia split the macula, and this appeared in conjunction with a new or "pseudo-macula." The preservation of central vision in this case may be explained by various hypotheses, such as a psychological reorganization of visual function in the remaining cortex, a diffuse representation of the macula, or by the formation of a new functional macula. The theory of bilateral representation of the cortical macula is not supported by this case because amputation of the entire occipital lobe resulted in a shifted macula-splitting hemianopia. The area of preserved vision was the result of a shifting of the macula—the inner border of the hemianopia being a straight line and not a semicircle.

Case 7.—The patient was a 20-year-old male who had been suffering from severe frontal headaches for three years. Two years before admission he had been fitted with glasses because of visual difficulties, but was not benefited. The

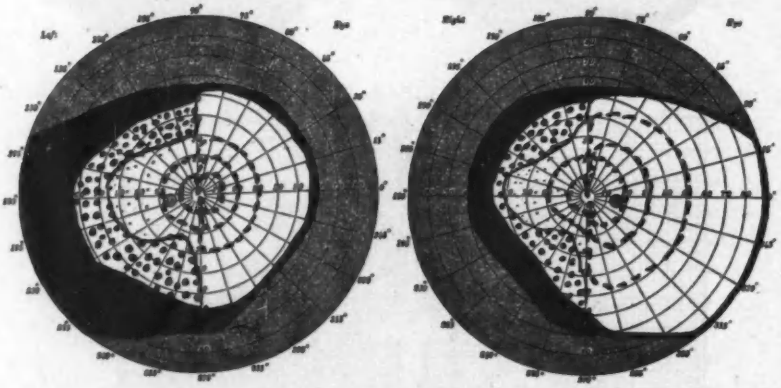

FIG. 8.—Incomplete left homonymous hemianopia. The solid black indicates an absolute scotoma. Heavy dots represent the area visualised by a 4 mm. test object. Small dots represent the zone visualized by a 1 mm. test object. Note the sector defects as outlined by the heavy dots. Dash lines represent borders for colour vision, concentrically 10, 4 and 1 mm. test objects. There is a macula-splitting hemianopia for green 1 mm. object.

physical examination in the hospital revealed a bilateral low grade papillœdema and an incomplete left homonymous hemianopia. A ventriculogram was performed and a large cyst in the right parieto-occipital region was outlined. At

operation, a hæmangioma was removed from the lateral surface of the right occipital and parietal lobes. After operation, a left homonymous hemianopia was found. The patient recovered without further complications and has remained well.

Perimetric examination performed six years later showed an incomplete left homonymous hemianopia for form with tendency to sector defects (fig. 8). With varied sized test objects the defect was made more apparent. The colour hemianopia was even more pronounced. There was only a relative sparing of vision in the central area.

Comment.—The hemianopia observed in this patient who had a lesion of the optic radiation in the occipital lobe is not different from the type of hemianopia seen in patients with lesion of the radiation in the temporal lobe. The field defect is most pronounced in the periphery but the central area is relatively equally affected. An interesting finding was the tendency to the formation of sector scotomata in the upper and lower fields of vision. This was particularly apparent with smaller sized test objects.

Some observers maintain that macular vision is widely represented in the occipital cortex (Fox and German, 1936). The anatomic evidence of Poliak (1932), however, favours the principle of a spatially organized projection system in the visual pathways. According to his studies of myelin sheath degeneration of the optic radiation, a wide cortical representation of the macula does not exist. Poliak admits that he did not examine the axis cylinders or the numerous fibre connections which exist in the cortex and subcortex. A consideration of the latter reveals that after the macular fibres reach the occipital lobe, they aborize and make wide and intricate associations with different parts of the cortex. It is well known that the end ramifications of nerve fibres partially overlap. This principle of overlapping of nerve paths has been found by Lorente de No (1934) to be a " general law of structure of the nervous system." In his discussion of point-to-point relationship in the visual system, Lorente de No stated that " each point of the retina is projected into a larger area of the cortex because the arborizations, protoplasmic as well as the axonal ones, are extensive, and therefore impulses set in any point of the retina may be transmitted to a larger area of the cerebral cortex. However, assuming that the neuron is a summation apparatus which reaches threshold excitation only when a certain number of its synapses are active, it becomes evident that physiologically the projection of the retina on the cerebral cortex may be point-like." The visual cortex may be so organized that each integral part receives impulses from all parts of the retina but in a differential manner. Thus there may well be a wide representation of the

macula in the occipital cortex in which the predominant number of impulses of macular origin reach the most posterior part of the striate area while the remainder enter other parts of the cortex. At the same time, fibres from the peripheral retina are predominantly represented in the anterior part of the area striata (Spence and Fulton, 1936) and a much smaller number connect with the occipital pole or cortical macula. Theoretically, destruction of the most posterior striate cortex alone should produce a corresponding homonymous hemianopic macular scotoma. If, however, the adjacent subcortical association or optic radiation fibres going to other parts of the cortex are involved in addition, then the resultant defects would be more widespread.[1] A reduction in the visual function of the entire homonymous field would follow. Since the acuity of the peripheral field of vision is low, any slight impairment of function representing the periphery would produce corresponding scotoma, which, in association with the homonymous central field defect, should result in a macula-splitting homonymous hemianopia. This, however, did not occur; some macular vision remained. If any fibres reach any part of the remaining visual cortex, there will be some preservation of central vision. Each integral part of the visual cortex may be so organized that impulses reach the cortex from all parts of the retina. Here they are integrated in patterns in which central vision assumes the highest acuity and peripheral vision the lowest. This, of course, would result in a markedly contracted homonymous field, thus giving a picture of homonymous hemianopia with relative sparing of the macula.

These hypotheses lead us to the theory of formation of a new "functional macula" postulated by Fuchs (1920) and supported by Goldstein (1925). This theory postulated a redistribution of energy in the intact portions of the visual field about a new functional centre of brightest vision, the "pseudo-fovea." This functional entity does not coincide, as in the normal field, with the fixation point but shows a displacement towards the side of preserved vision. The position of this "pseudo-fovea," accordingly, would correspond with an eccentric spot of the still functioning part of the retina (Kanzer and Bender, 1939). With lesions of the occipital lobe

[1] It must be remembered that a tumour of the occipital lobe which causes symptoms involves not only the cortex but the subcortex and optic radiation as well. The physiological changes produced in these instances cannot be the same as in lesions of the cortex alone. Pure cortical lesions are extremely rare. The homonymous scotomata that result from lesions in the calcarine area may be attributed not only to the involvement of the cortex but to the implication of the immediate subcortical association fibres as well.

the patient may develop a new fixation point.[1] Perimetric examination in these cases will reveal an area of preserved vision on the hemianopic side of the fixation point. Careful examination, however, will show that the zone of preserved vision is not circular but linear in the vertical meridian. This is due to the displacement of the macula-splitting hemianopia to one side by the formation of a new central fixation point. Such a shift is of significance in estimating the extent of the "macula-sparing" and in determining the peripheral boundaries of the visual field. This factor is neglected in performing the usual tests for the peripheral field of vision, which require an enforced static position of the eye that does not permit the manifestation of important visual psychomotor disturbances resulting from lesions in the parieto-occipital region (Fox and Holmes, 1926; Hoff and Pötzl, 1933). Nevertheless, the psychomotor adaptation of the eye necessarily assumes an important rôle in the total visual process, determining not only the direction of attention but the form of perceived objects (Kanzer and Bender, 1939). Such considerations emphasize the necessity of regarding vision as a total function rather than as a strictly determined correlate of anatomic pathways.

Discussion.

Presumably, in our cases with tumour involving the occipital pole ("cortical macula"), the preservation of central vision is due to a shifting of function to another part of the calcarine cortex (the most anterior part) or to a widespread representation of the macula in the cortex, or both. We do not believe that the cortical macula is bilaterally represented. In cases of tumour involving the optic radiation in the temporal lobe, other factors must be considered. The dynamics of the hemianopias in these cases may be accounted for by the anatomical characteristics of the geniculo-calcarine pathway and by the progressive nature of the disease process which occurs with brain tumours.

The internal structure of the visual pathway has been ascertained by the method of myelin sheath degeneration (*see* fig. 9). Brouwer and Zeeman (1926), Putnam and Putnam (1926) made small lesions in the retina of

[1] Fixation is brought about by directing the eye so that the object is in line with the visual axis, its image falling upon the fovea. During fixation the eye is not absolutely steady, but makes constant slight excursion, so that the fovea traverses the different parts of the objects regarded and produces a synthetic picture. If there is a disturbance in central vision, such as occurs with macula-splitting hemianopia, the retina of each eye will move into such a position as to obtain the best fixation possible, thus forming a new fovea.

monkeys and rabbits and traced the degeneration along the infrageniculate course. Similarly Poliak (1932) studied the degeneration between the lateral geniculate body and the occipital lobe cortex. Each investigator found

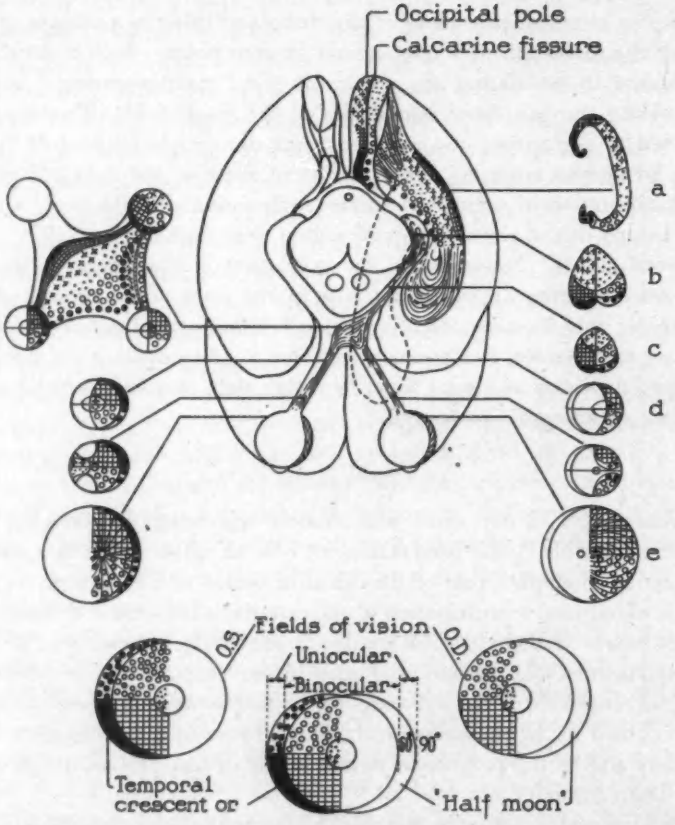

FIG. 9.—Schema illustrating the probable course of the afferent visual pathways at different levels of the nervous system and their projected visual fields. Reconstructed and modified from the works of Brouwer and Zeeman (1926), Wilbrand (1926) and Poliak (1932).

every point of the retina to be projected throughout the central visual system in a definite order. In a general way the arrangement of the dorsal, ventral, temporal and nasal fibres of the retina maintained their respective positions throughout the entire retino-geniculo-calcarine pathway. In the

optic radiation the fibres arrange themselves in a vertical plane (*see* fig. 9). The macular fibres are in the middle of the geniculo-calcarine path; the fibres from the upper retina (illustrated by crosses in fig. 9) traverse the upper half, and the fibres from the lower retina (represented by small dots) course through the lower half of the vertical rim of the optic radiation. The fibres peripheral to the upper macular region (indicated by cross-hatched lines) are placed more superiorly, and the fibres peripheral to the lower macular region (illustrated by circles in the figure) are located more inferiorly in the radiation. The most peripheral fibres, derived from the upper and lower halves of temporal crescents and representing uniocular vision, are on the extreme upper (solid black) and lower (heavy dots in figure) edges of the vertical rim respectively. The number of optic fibres representing different parts of the field of vision and the area projected by them in the radiation decreases from the centre toward the periphery. The macular fibres are largest in number and cover a greater area than the peripheral fibres. The "crescent" fibres are fewest in number and cover the least area. The change is gradual, there being no sharp demarcation between two closely adjacent points in the field of vision.

The disturbances produced by tumours in the temporal or occipital lobes are rarely limited to the confines of the tumour itself. In cases of tumour of the brain implicating the optic radiation, the function of the entire geniculo-calcarine pathway would be impaired by œdema surrounding the neoplasm. In view of the anatomical facts cited, the earliest disturbances may be expected in the field of vision subserved by fibres which conduct the lowest visual acuity or where the fibres are fewest in number and occupy the smallest area. Actually, the regions subserved by the peripheral temporal fibres are involved first (Bender and Strauss, 1936); these fibres are fewer in number and cover less area than the fibres representing the central fields. As the pathological processes progress, an increasing number of fibres are involved and a corresponding defect from the periphery to the centre becomes manifest. Thus a pathological link between the anatomical and clinical finding is provided.

Efforts made with several patients to elicit minute discrete scotomata in the area of preserved central vision were unsuccessful: there were no such scotomata. Such an absence of scotomata with lesions of a spatially organized optic radiation suggests that this structure operates as an entity rather than as a conglomeration of separate visual units. Inasmuch as the function of the entire radiation is impaired, all the individual components are necessarily affected.

In conclusion, it should be emphasized that the studies on homonymous

hemianopias associated with tumours of the brain permit the progressive nature of the visual disturbance to be followed. In this way, certain factors emerge which cannot be determined when the observations are limited to cases in which lesions have occurred suddenly, such as trauma and cerebro-vascular accidents. In a gunshot wound of the brain or in an occlusion of one of the cerebral vessels, the resulting homonymous hemianopia appears immediately and as time goes on there is regression of the hemianopia. We have followed patients with homonymous field defects associated with thrombosis of middle cerebral artery. When improvement occurred, central vision returned first and then enlarged in area peripherally. In tumours of the brain, however, the reverse is true. The homonymous hemianopia sets in gradually, unless, of course, there is an accompanying occlusion of a vessel. The field defect begins in the periphery and advances centrally. The rate of progression depends on the rate of the tumour growth and of alteration in the surrounding tissues. Regression is rare, because of the progressive nature of the neoplasm.

In inflammatory lesions, that is, non-suppurative encephalitis, we may follow the complete cycle of development and regression of a homonymous hemianopia (Bender and Strauss, 1937). In these instances the lesion develops and regresses slowly and thus allows of frequent examination of the fields of vision.

Summary.

Observations on cases of progressive hemianopia associated with tumours of the brain indicate that there is a concomitant relationship between visual acuity, colour vision and peripheral defects in the visual field. So-called "macula-sparing" in cases of homonymous hemianopia is found to be a stage in the development of a complete hemianopia, the defects beginning in the periphery of the field and gradually spreading toward the centre. Careful examination of the "preserved" field of vision will often disclose diminished visual acuity and impairment of colour vision, indicating an early disturbance in the function of the visual pathways. These findings suggest a functional integrity of the optic radiation, a hypothesis which finds further support in the fact that examination fails to reveal minute scotomata in the areas of preserved vision such as should be found with a diffusely involved organization of discrete optic units. This conception of functional unity of the optic radiation is useful in explaining the sparing of central vision irrespective of the localization of the lesion within the radiation and provides an alternative, in many cases, to a hypothesis of bilateral representation of the macula. Criteria for judging

the extent of macula-sparing are discussed and the observation made that instances of complete loss of macular vision resulting from brain tumour are very rare.

REFERENCES.

ALLEN, I. M. (1930), *Brain*, **53**, 194.

BENDER, M. B., and STRAUSS, I. (1937), *Arch. Ophth.*, **17**, 765.

BROUWER, B. (1936), "Erdrnakungen der Sehstrahlung und der Sehrinde." Handbuch der Neurologie (O. Bumke and O. Foerster), Julius Springer. Berlin, **61**, 505.

—— and ZEEMAN, W. P. C. (1926), *Brain*, **49**, 1.

CUSHING, H. (1921), *ibid.*, **44**, 341.

FOERSTER, O. (1929), *J. Psychol. u. Neurol.*, **39**, 463.

FOX, J. C., and GERMAN, W. J. (1936), *Arch. Neurol. and Psych.*, **35**, 808.

—— and HOLMES, G. (1926), *Brain*, **49**, 333.

FUCHS, W. (1920), *Ztsch. F. Psychol.*, **84**, 67.

GLOBUS, J. H., and SILVERSTONE, S. M. (1935), *Arch. Ophth.*, **14**, 325.

GOLDSTEIN, K. (1925), *Arch. f. Psych.*, **74**, 370.

HOFF, H., and PÖTZL, O. (1933), *Jahrb. f. Psych. und Neurol.*, **50**, 35.

HOLMES, G. (1918), *Br. J. Ophth.*, **2**, 353.

——(1931), *Brain*, **54**, 470.

—— and LISTER, W. (1916), *ibid.*, **39**, 34.

HORRAX, G., and PUTNAM, T. (1932), *ibid.*, **55**, 499.

KANZER, M., and BENDER, M. B. (1939), *Arch. Ophth.*, **21**, 439.

LENZ, G. (1921), *Ztschr. Ges. Neurol. u. Psych.*, **71**, 135.

LORENTE DE NO, R. (1934), *J. F. Psychol. u. Neurol.*, **46**, 113.

MAGITOT, A., and HARTMANN, E. (1926), *Bull. Soc. d'Ophth. de Paris.* Pp. 427 and 639.

PENFIELD, W., EVANS, J. P., and MACMILLAN, J. A. (1935), *Arch. Neurol. and Psych.*, **33**, 816.

PFEIFFER, R. A. (1925), "Myelogenetische Untersuchungen ueber den zentralen Abschnitt der Sehleitung." In Foerster, O., and Willmanns, K. Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie. Berlin, Julius Springer.

POLIAK, S. (1932), "The Main Afferent Fibre Systems of the Central Cortex in Primates." Univ. of Cal. Publications in Anatomy. Univ. Cal. Press, vol. 2, Berkley, Calif.

PUTNAM, T. J., and PUTNAM, I. K. (1926), *Arch. Neurol. and Psych.*, **16**, 1.

——(1926), *ibid.*, **16**, 566.

SPENCE, K. W., and FULTON, J. F. (1936), *Brain*, **59**, 35.

TRAQUAIR, H. M. (1938), "An Introduction to Clinical Perimetry." C. V. Mosby Co., St. Louis, Mo.

WECHSLER, I. S. (1933), *Arch. Ophth.*, **13**, 957.

WILBRAND, H. (1907), *Klin. Monatsbl. f. Augenheilk.*, **4**, 1.

——(1926), *Ztschr. f. Augenheilk.*, **59**, 135.

BLOOD CHANGES IN DYSTROPHIA MYOTONICA

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ALTHOUGH there has been a considerable amount of research into creatinine and creatine changes in blood and muscle in cases of dystrophia myotonica very little attention has been directed to changes in potassium in the blood or muscle. (Recently Leulier and Pommé (1934, 1935) and Cumings (1939*b*) have estimated the potassium content of muscles from patients with myotonia. The last author showed that muscles from affected areas contained a lower potassium content than normal muscles. It seemed that certain investigations into the serum potassium might yield results of value. Allott and McArdle (1938) have shown that large doses of glucose and injection of insulin reduced the serum potassium and at the same time produced paralysis in patients with familial periodic paralysis. Similar procedures to those used by these authors were undertaken in two patients with myotonia. Potassium was estimated in the serum (Cumings, 1939*a*), and at the same time some other substances were also estimated. These were calcium, inorganic phosphorus, chlorides, magnesium, urea and sugar (using methods as used in a previous investigation (Cumings, 1938)). Blood was taken before and after the administration of glucose and insulin.

The results obtained showed no significant changes between the two blood samples in either patient. The serum potassium contents were 22·97 mg. per cent. and 16·24 mg. per cent. before, and 19·37 mg. per cent. and 17·63 mg. per cent. after the experiments respectively. The sugar level fell slightly in both patients, and there was a slight rise (less than 10 per cent.) in the chloride level between the two samples of blood in both patients. The other constituents examined did not alter at all.

EXERCISE EXPERIMENTS.

The effect of exercise on the serum potassium was then studied. The exercises consisted of fairly rapid walking, together with simple arm exercises for a period of half an hour, and these were conducted as far as possible at the same time of day in every case. Blood was taken before and after the period of exercise.

The patients examined consisted of eleven cases of myotonia, two of

myasthenia gravis, two with loss of muscular power comparable to the loss found in the patients with myotonia, and two perfectly normal male subjects.

Plasma chlorides were determined on the first three cases of myotonia and on the two cases with muscular weakness, in case any alteration of total blood composition took place which could be detected by this means. There was no alteration at all in the chloride level before and after exercise.

Results.

The two normal subjects, the two patients with myasthenia gravis and the two patients with loss of muscular power showed no significant alteration in the serum potassium levels before and after exercise. The two patients with myasthenia gravis had slightly low potassium contents. They were 15·08 mg. per cent. and 18·27 mg. per cent. and these fell to 14·15 mg. per cent. and 16·53 mg. per cent. respectively.

The eleven cases of myotonia could be divided into two groups on clinical examination. The first group consisted of four patients who showed marked myotonia with no wasting or only wasting of a slight degree. The second group of seven patients showed very slight myotonia with definite wasting. The presence of myotonia and of muscular atrophy in the face and neck was disregarded as the exercises only involved muscles of the extremities.

Table I shows the results in the first group together with indications as to the degree of myotonia and wasting.

TABLE I.

Patient	Degree of myotonia	Degree of wasting	Potassium before exercise in mg. %	Potassium after exercise in mg. %
Mr. B.	++	−	15·78	9·51
Mr. S.	++	−	24·84	17·01
Mrs. V.	++	±	25·2	14·4
Miss B.	+	±	24·01	19·14

Table II gives the results found in the second group.

TABLE II.

Patient	Degree of myotonia	Degree of wasting	Potassium before exercise in mg. %	Potassium after exercise in mg. %
Miss D. . ..	±	+	14·15	15·54
Mr. D. ...	±	±	15·78	16·94
Mr. R. B. ...	±	±	13·22	13·92
Mr. H.	±	±	17·92	17·4
Mr. J. L. McD. ...	+	++	21·23	21·58
Mr. J. McD. ...	±	+	15·9	24·1
Mr. E. McD. ...	±	±	18·62	18·27

It is seen that in all four patients in the first group there is a very definite fall in the serum potassium after exercise, although this is less marked in the last case, which showed the least amount of myotonia in this group. Three of these patients had normal resting potassium levels. Patients in the second group, however, show no alteration in the potassium level after exercise, but many of them show a low resting level. All except one (Mr. D.) in this second group are cases of long duration of the disease.

Fenn and Cobb (1936) have shown that during muscular contraction there is a loss of potassium from muscles of animals. The two normal subjects showed no appreciable alteration in the potassium level after exercise, but it seems hardly likely that the changes shown by Fenn and Cobb could be demonstrated in the circulating blood in man, although an increase of potassium has been shown in the perfused fluid obtained from fibrillating heart muscle (Kehar and Hooper, 1935). Loss of muscular activity and power cannot account for the fall in serum potassium after exercise in the first group as the two patients who had muscular atrophy comparable to that in the cases of myotonia showed no alteration in their potassium levels, and this is in agreement with the finding in the second group, who also had quite marked wasting. Similarly, Fenn (1938) has shown that decrease of circulation due to muscular contraction of stimulated muscles results in a diminution of the potassium loss from these muscles, but this would affect the results in both groups equally. It would seem, therefore, that this lowering in potassium levels after exercise is only to be found in relatively early cases, in conjunction with a considerable degree of myotonia.

It has been shown by one of us that the resting muscle potassium in myotonia is low, and it would seem highly probable that the lowering of the serum potassium after exercise is accompanied by an increase in the muscle potassium. If this is correct the greater ability to use affected muscles after mild exercise is either due to or is accompanied by a more normal level of potassium in muscle.

It is with pleasure that we thank the staff of the National Hospital for permitting us to utilize patients under their care.

Summary.

Blood changes in dystrophia myotonica have been studied, especially the effect of exercise on the potassium content. It has been shown that exercise causes a decrease in the serum potassium in patients with marked myotonia and little atrophy.

Possible explanations of this change have been discussed.

REFERENCES.

ALLOTT, E. N., and MCARDLE, B. (1938), *Clin. Sc.*, **3**, 229.
CUMINGS, J. N. (1938), *J. Neuro. & Psych.* (New series), **1**, 61.
——(1939*a*), *Biochem. J.*, **33**, 642.
——(1939*b*), *Brain*, **62**, 153.
FENN, W. O. (1938), *Amer. J. Physiol.*, **124**, 213.
FENN, W. O., and COBB, D. M. (1936), *Ibid.*, **115**, 345.
KEHAR, N. D., and HOOPER, D. R. (1935), *Ibid.*, **112**, 301.
LEULIER, A., and POMMÉ, B. (1934), *Presse Médicale*, **42**, 1353.
——(1935), *C. R. Soc. Biol.*, **119**, 201.

A BIOCHEMICAL STUDY OF CEREBRAL TISSUE, AND OF THE CHANGES IN CEREBRAL ŒDEMA.

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Introduction.

Studies of the physiochemical changes in cerebral œdema have been few and have been confined to general "brain swelling" as shown by a diminution from the normal in the difference between skull capacity and brain volume. Such alterations, for example, have been described as occurring in some forms of psychosis, epilepsy, cerebro-vascular disease and general toxæmias. Using material of this kind and estimating the differential ratio of skull capacity to brain volume to determine the presence of cerebral œdema or atrophy, neither Schluter and Nevin (1932) nor Alexander and Looney (1938) could show any increase in the total water content of "œdematous" brain compared with normal or "atrophied" brain. The former found the average specific gravity of the swollen brains to be a little lower than the normals, and the latter found an increased water combining capacity when brought into solutions of weak NaCl. They concluded that "œdema of the brain cannot be expressed in terms of total water content."

There are on record no investigations into the fluid changes in the local œdema, which has long been recognized to occur round tumours and abscesses, and in which Greenfield (1939) has recently described characteristic histological changes. The present study is based on an analysis of the water, Na, K, Cl, and P contents of œdematous brain tissue associated with cerebral tumours, using corresponding tissue from the opposite hemisphere as a control. As there are only a few scattered references in the literature to chemical estimations of brain electrolytes, the findings in a series of cases dying of other cerebral and non-cerebral conditions are first discussed.

Methods.—(i) Total water content: From 1 to 10 grm. of grey and white matter were dissected out, freed from membranes and placed in a silica crucible. The tissue was rapidly cut up and spread out in the crucible with a dry knife and forceps, weighed with the lid on and then dried to a constant weight. Controls showed that 110° C. overnight (= 18 hours) achieved this most conveniently.

Controls using small pieces from 0·5 grm. upwards gave the same results to within 1 per cent. as larger pieces up to 10 grm.

(ii) Chloride: The method of McCance and Shipp (1933) was used, taking about 0·2 grm. dry brain tissue and boiling with 5 c.c. conc. nitric acid for four to six hours.

(iii) Potassium and sodium: About 0·1 grm. of dry tissue was ashed with conc. HNO_3, and aliquot portions taken for estimations of potassium as described by Cumings (1939). Other portions of the same ash were used for estimating sodium by the method of Woefel (1938).

(iv) Total phosphorus: About 0·2 grm. of dry brain was heated with 1 c.c. of conc. HNO_3, and 1 c.c. of conc. H_2SO_4, if necessary repeating with more HNO_3, till digestion was completed. After neutralizing with 5 c.c. of 10 per cent. NaOH and adding 1 c.c. of 20 per cent. Na_2SO_3, the phosphorus in the digest was estimated by the method described by Fiske and Subbarrow (1925).

Water and Electrolytic Contents of Brain Tissue.

Table I shows the total water content in an unselected series of cases coming to autopsy at the National Hospital, excluding those having a naked-eye appearance of œdema or hydrocephalus of a degree severe enough to produce obvious cerebral atrophy. The majority had intracranial

Table I.—Water Content of Normal Brain Tissue.

(grm. H_2O per 100 grm. whole tissue.)

	No. of cases	Range	Average
White matter (centrum ovale) ...	34	67·5–75·0	70·7
Internal capsule	4	69·1–71·6	70·1
Corpus callosum	6	74·1–76·7	75·7
White matter of cerebellum ...	2	70·2–71·1	70·6
Cerebral cortex	31	81·0–85·5	84·3
Thalamus	6	73·4–76·8	75·1

lesions, others had diseases of the spinal cord, and a few died of diseases affecting organs other than the central nervous system. The average water content and range of variation agree with previously published figures of material taken from cases dying in general hospitals for diseases not specially related to the nervous system. Moreover three of our cases, in which there was no clinical or pathological evidence to suggest disease of the central nervous system, gives similar results (white matter 69·1 per cent., 70·2 per cent. and 74·6 per cent. and grey matter 82·3 per cent., 83·6 per cent. and 85·5 per cent. respectively) suggesting

that the figures in Table I represent average findings for human brain tissue in the cadaver. There is a certain range of variation, particularly in the white matter. Such a variation is common to all tissue analyses and is not peculiar to brain. Thus Cumings in his analysis of muscle (1939) found a variation in water content ranging from 66·4 per cent. to 87·3 per cent. in forty cases. While the mode of death, recent fluid intake, operation hæmorrhage, shock, therapeutic salines, general wasting and toxæmias may account for some of this variation, there is probably a considerable variation in different specimens of healthy living tissue, since the variation in Cuming's figures for muscle applied to biopsy material. Since the electrolytic content is related to the amount of water, it is to be expected that a similar variation will also be found in the quantity of these solutes. Most of the cases in this series were kept in cold storage till autopsy. No correlation could be found between the water or electrolytic content and the length of time after death. In two cases, however, not included in this series, in which the bodies had been kept over forty-eight hours at room temperature and visible post-mortem degeneration had developed, there was a considerably higher percentage of water (white matter 84·3 and 89·2 per cent. respectively).

From Table I it will be seen that the cortical grey matter (average 84·3 per cent.) contains considerably more water than the white matter, both of the cerebral (70·7 per cent.) and the cerebellar (70·6 per cent.) hemispheres, while intermediate values are found for the thalamus (75·1 per cent.) and corpus callosum (75·7 per cent.).

In Table II the chloride, potassium, sodium and phosphorous contents

TABLE II.—ELECTROLYTIC CONTENT OF NORMAL BRAIN TISSUE.

H_2O		Chloride		Sodium		Potassium		Phosphorus	
Average		Range	Average	Range	Average	Range	Average	Range	Average
White matter (centum ovale)	70·7%	93–154 (6)	128	99–196 (14)	158	184–281 (19)	232	332–390 (9)	366 [1250]*
Cerebral cortex	84·3 %	210–220 (6)	215	159–215 (9)	193	210–244 (8)	228	195–210 (4)	203 [1290]*
Cerebellum (white matter)	70·6%	(2)	109	(2)	120	(2)	223	(2)	376 [1280]*

Mgm. per 100 grm. whole brain tissue.

Figures in ( ) equal number of cases investigated.

* Figures for phosphorus are also expressed in mgm. per 100 grm. of dry tissue and are shown in [ ].

of grey and white matter are tabulated. There is a considerable variation in the amount of these solutes in different samples, a variation which, as has already been mentioned, is also found in other tissues such as blood and muscle. The chloride and sodium are present in larger amounts in the grey matter, which contains the greater percentage of water, while the amount of potassium is about the same in grey and white matter. The phosphorus, however, which being chiefly in organic combination, is related rather to the solids than the water, is present in larger amounts in the white than the grey matter, when considered in relation to whole tissue, but the amounts are almost the same when expressed as a percentage of the dry weight. No appreciable difference is found between the electrolytic contents of the white matter of the cerebral and cerebellar hemispheres.

These figures represent an analysis of the whole tissue—being the sum of intracellular and extracellular components. The composition of tissue cells themselves cannot, with the single exception of blood-cells, be determined by direct analysis, because they cannot be separated from the interstitial substance which surrounds and connects them. The existence of the latter cannot be questioned; its volume and character defy direct measurement. From indirect evidence, however, there are convincing reasons for believing, as Peters shows in his detailed discussion of "Body Water" (1935) that this interstitial fluid, like lymph, œdema fluid and serous transudates, resembles a colloid-free ultra-filtrate of serum. All these fluids have a similar electrolytic pattern to serum. The only difference is a slightly higher Cl and a lower K content, and this is related to the difference in the amount of protein. This is in accordance with the Gibbs-Donnan principle which determines the ionic distribution across a semi-permeable membrane, and is maintained when the two fluids are dialysed *in vitro* against one another across a membrane impermeable only to lipoids and proteins. Furthermore, in the case of muscle a large amount of evidence has accumulated to support the belief, now generally accepted, that the chloride is confined to the extracellular spaces. This has recently received confirmation from Gersh (1938) who stained the chlorides histochemically.

In Table III are set out the intra- and extracellular constituents of muscle, taking the interstitial fluid to be a protein-free ultra-filtrate of serum containing all the chlorides. In 100 grm. of muscle, 15·5 grm. of the total 72·8 grm. of water are intracellular and 57·3 grm. are extracellular. Furthermore, there is only a very small amount of sodium and a large amount of potassium within the muscle cell.

In the case of cerebral tissue the Na/Cl ratio is very high—3·12 and 2·28 for white and grey matter respectively. This, in contrast with the ratio for muscle (Na/Cl = 1·44) where the Na is almost all extracellular, greatly exceeds that for serum filtrate (Na/Cl = 1·33). This large excess of Na must lie within the cells if the interstitial fluid is to resemble a serum filtrate.

TABLE III.—CONSTITUENTS OF "CHLORIDE" AND "NON-CHLORIDE" SPACES.
Milliequivalents %.

	Water (grm. %)	Chloride	Sodium	Potassium	Phosphorus	Na/Cl ratio
SERUM.						
Ultra-filtrate ...	100	11·1	14·8	0·25	0·32	1·33
MUSCLE.						
Whole	72·8	1·72	2·49	7·18	4·88	1·44
Chloride space (extracellular)	15·5	1·72	2·29	0·04	0·05	
Non-chloride space (intracellular)	57·3	0	0·2	7·14	4·83	
CEREBRAL *White Matter.*						
Whole	70·7	2·19	6·88	5·95	11·8	3·12
Chloride space (? extracellular)	18·3	2·19	2·71	0·05	0·06	
Non-chloride space (? intracellular)	52·4	0	4·17	5·9	11·74	
CEREBRAL *Grey Matter.*						
Whole	84·3	3·68	8·40	5·85	6·65	2·28
Chloride space (? extracellular)	33·0	3·68	4·88	0·08	0·11	
Non-chloride space (? intracellular)	51·3	0	3·52	5·77	6·54	

The figures for serum are taken from Peters' Body Water (1935); those for muscle were kindly supplied by Dr. J. N. Cumings, except for the Na and Cl estimations, which were carried out by the author. The contents of the "chloride space" are calculated by allotting amounts of Na, K and P to the chloride in the same proportions as they occur in a serum filtrate. The remainder are allotted to the "non-chloride space." For the purpose of the calculation serum filtrate is taken as containing a negligible quantity of solids, i.e. is 100% water.

In Table III brain tissue has also been divided up into what we may term "chloride" and "non-chloride spaces" in the same manner as that applied to muscle. It is found that: (*a*) White matter contains 70·7 per cent. grm. water, 18·3 grm. of which are in the "chloride space" and 52·4 grm. in the "non-chloride space." (*b*) Grey matter contains 84·3 per cent. grm. water 33·0 grm. of which are in the "chloride space" and 51·3 grm. in the "non-chloride space."

Now in the case of muscle, as has been already pointed out, the "chloride space" can be regarded with confidence as representing the extracellular tissue. In cerebral white matter the amount of "chloride space" is of the same order as in muscle and is much less than in grey matter, so that we cannot allot any considerable proportion of the chloride to the intracellular tissue of the white matter without reducing the interstitial spaces to a much smaller percentage than has been found in other tissues. It is probable, therefore, that these figures give the approximate proportions of intracellular and extracellular fluids in white matter. In the case of grey matter also it seems likely that the "non-chloride space" represents the intracellular substance, as it appears to do in muscle and white matter, since the "non-chloride space" contains K and Na in approximately the same quantities as in the "non-chloride space" of white matter. It would, however, require confirmation by histo-chemical staining of the chlorides before one could accept with certainty that these figures for the "non-chloride spaces" do represent an analysis of the intracellular tissue.

TABLE IV.—THE COMPOSITION OF TISSUE CELLS.

	Water (grm. % of cell tissue)	Na (Milliequivalents per 100 grm. of cell water)	K	Cl	Solids (grm. % of cell tissue)	P (Milliequivalents per 100 grm. of solids)
Cerebral white matter 81·7%*	64·1	7·8	11·3	0	35·9	40·0
Cerebral grey matter 67·0%*	76·5	6·9	11·2	0	23·5	41·7
Muscle ... ... 84·5%*	67·8	0·29	12·4	0	32·2	17·7
Red cells ... ... 44·0%*	66·2	2·5	11·4	7·4	33·8	5·0

* = grm. of intracellular substance (fluids and solids) per 100 grm. of whole tissue. For the purpose of this calculation the interstitial fluid is taken as containing a negligible quantity of solids, i.e. water = 100%.

In Table IV the constituents of the "non-chloride spaces" of white and grey matter are set out in detail, thus showing the probable composition of the tissue cells. In the same table they are contrasted with muscle and red cells, the only other tissues for which figures are available. In white and grey cerebral tissue there are 7·8 and 6·9 milliequivs of sodium per 100 grm. of cell water respectively, whereas in red cells there is only a small quantity (2·5 milliequivs %) and in muscle cells a negligible quantity (0·29 milliequivs %). The amount of potassium (11·3 and 11·2 milliequivs %, in white and grey matter respectively) is approximately equal to the amount in both blood (11·4 milliequivs %) and muscle (12·4 milliequivs %) cells. Phosphorus is present in very large amount in brain cells, being about equal in grey and white matter (40·0 and 41·7 milliequivs %

respectively) when expressed as a percentage of the solids; this quantity is over twice that found in muscle cells (17·7 milliequivs %), and eight times that in red cells (5·0 milliequivs %).

Cerebral Œdema.

Six cases of localized cerebral œdema associated with cerebral tumours and one related to a recent hæmorrhage were examined. In a cut section the white matter in the œdematous areas has a softer, more fluid and more swollen appearance to the naked eye than normal, while the grey matter is not obviously altered. This watery appearance is especially evident when a small piece is cut up in a crucible and a striking contrast is found in its soft consistency—in some cases almost resembling junket—and the tough normal white matter. However, in spite of the wet appearance, fluid does not actually drip or run from œdematous brain as is stated in many text-books. All methods, including draining, suction, filtering and squeezing in fine wire gauze and silk bags, failed to separate any fluid for analysis.

Table V.—Water Content of Œdematous Contrasted with Normal Brain Tissue

Case No.	White matter Centrum ovale		Grey matter cortex		Corpus callosum	Internal capsule (from side of the lesion).	Thalamus
	N-O.T.	O.T.	N-O.T.	O.T.			
1	68·6	80·1	81·0	82·7			
2	69·7	82·1	82·5	83·4			
3	68·0	78·6					
4	68·9	78·8	83·7	82·0	75·4	69·3	
5	71·8	86·0	83·6	84·5	73·3		
6	68·8	83·7	82·4	82·8	75·3	71·6	74·6
7	71·1†	83·6†					
Average	69·6	81·8	82·6	83·1	74·7 (75·7)*	70·4 (70·1)*	74·6 (75·1)*

Water in grm. %.

* Figures in brackets = average normal values from Table I.
† Cerebellar white matter.
N-O.T. = Non-œdematous tissue.
O.T. = Œdematous tissue.

In Table V the total water content of the seven specimens of œdematous tissue is shown and is contrasted with corresponding tissue from the opposite hemispheres. A marked increase is found in the water content of the white matter on the side of the lesion (average, 81·8 per cent.) compared with tissue taken from the opposite side (average, 69·6 per cent.). There is no material difference between the grey matter of the cortex on the two sides. Moreover, a more detailed analysis in three of the cases suggests that the changes are restricted to the centrum ovale and do not involve the corpus callosum, internal capsule or thalamus (*see* Table V).

An analysis of the Na, Cl, K and P contents of tissue from the normal and œdematous sides was carried out with a view to determining the nature of the fluid changes. The values for white matter are shown in Table VI. There is a very large increase in the amount of Cl in the œdematous tissue compared with normal (average 29·6 milliequivs % and 7·6 respectively), a large increase in the Na (58·9 per cent. and 27·0 per cent. respectively), a negligible change in the K (22 per cent. and 21·3 per cent. respectively) and a slight decrease in the P (35·6 and 40·6 per cent. respectively). In the grey matter, in which it has been shown that no changes in the fluid content occurred, analysis of these electrolytes showed no significant changes in the two cases examined.

In Graphs I, II and III the amounts of Cl, Na and K, respectively, are plotted against the amount of fluid associated with 100 grm. of dry tissue on the normal and abnormal sides of the seven cases. On each graph the continuous line is a straight line joining the average of the seven normal values with the average of the seven abnormal values. In the case of Na there is such a wide range in the figures for the different specimens of the normal tissue that each individual point is joined up with the corresponding point representing the Na value of the œdematous tissue taken from the same brain; the continuous line joins the average figures for the normal and abnormal sides. On each graph the interrupted line represents the calculated values that would be found if the increase in fluid were an addition of a colloid-free ultrafiltrate of serum; in other words were a simple increase in interstitial fluid.

From Graph IV, in which is shown a composite picture of the Na, K and Cl changes, it is seen that the Na and Cl increase with the increase in water in almost the same proportions as they would do if the extra fluid was an addition of a serum filtrate. Moreover, the K which is present in only very small amounts in serum, is increased by a negligible amount.

The following figures in milliequivs % contrast the amount of these solutes in a serum ultrafiltrate and in the "œdema fluid," the composition of which is calculated from the difference between the electrolytic contents of the normal and pathological tissues.

	Na	Cl	K	Na/Cl ratio.
Serum filtrate	14·8	11·1	0·25	1·33
"Œdema fluid"	13·3	9·2	0·21	1·44

The composition of these two fluids is strikingly close, suggesting that in cerebral œdema, as in œdema in other tissues, there is an increase of the interstitial fluid in the extracellular spaces, derived from the circulating blood. Furthermore, in support of this, there is no increase in the

phosphorus (*see* Table VI), which is only present in serum in minute amounts. There is actually a slight but consistent decrease in the quantity of phosphorus. This probably is not large enough to be of significance, but may be associated with the breaking down of the complex organic compounds in the cell tissue of the white matter, associated with the degenerative processes which have recently been demonstrated histologically by Greenfield (1939).

TABLE VI.—ANALYSIS OF ŒDEMATOUS WHITE MATTER AND CORRESPONDING TISSUE FROM THE OPPOSITE HEMISPHERE.

Milliequivalents per 100 grm. of dried tissue.

Case No.	Water combined with 100 grm. dried (tissue)		Chloride		Sodium		Potassium		Phosphorus	
	N-O.T.	O.T.	N-O.T.	O.T.	N-O.T.	O.T.	N-O.T.	O.T.	N-O.T.	O.T.
1	200	303	7·2	21·5	19·5	39·0	24·0	27		
2	218	419	10·5	25·5	43·0	78·0	21·5	25	37·1	36·9
3	229	460	7·7	27·9	42·0	80·6	18·5	21		
4	213	380	7·3	24·0	30·0	60·0	22·0	21		
5	254	638	7·6	46·9	22·5	52·0	24·5	21	39·7	24·2
6	220	540	7·3	34·0	13·0	45·0	19·5	21	43·2	40·3
7	248	530	5·7	27·9	18·0	59·0	19·0	21	42·3	40·0
Average	226	467	7·6	29·6	27·0	58·9	21·3	22·0	40·6	35·6

N-O.T. = Non-œdematous tissue.
O.T. = Œdematous tissue.

In all the cases investigated in this series, there is a very great addition of œdema fluid in the white matter of the œdematous side. 100 grm. of cellular tissue are associated on the normal side with an average of 110 grm. of interstitial fluid, and on the œdematous side with 249 grm., representing an addition of 139 grm. œdema fluid.[1]

[1] These values can be readily calculated from the figures in Table III for normal brain, and Table VI for œdematous brain.

Normal Brain.—29·3 grm. solids + 18·3 grm. water in intracellular tissue are associated with 52·4 grm. extracellular fluid.

∴ 100 grm. of intracellular tissue are associated with $\frac{100 \times 52{\cdot}4}{29{\cdot}3 + 18{\cdot}3}$ grm. (which = 110 grm.) extracellular fluid.

Œdematous Brain.—100 grm. dry tissue are associated with 467 grm. fluid (extra and intracellular).

∴ 29·3 grm. solids + 18·3 grm. fluid in intracellular tissue are associated with $\frac{467 \times 29{\cdot}3}{100} - 18{\cdot}3$ grm. (which = 118·5 grm.) of extracellular fluid.

∴ 100 grm. of intracellular tissue are associated with $\frac{118{\cdot}5 \times 100}{29{\cdot}3 + 18{\cdot}3}$ (which = 249) grm. extracellular fluid.

Case 7 in Tables V and VI is an analysis of œdematous white matter related to a recent hæmorrhage of the cerebellum and exactly the same changes are found as in the cases associated with cerebral tumours, showing that the changes in cerebral œdema from both these conditions are similar.

In no case in the present series was there any evidence of a condition, in association with cerebral tumours, of brain swelling not due to hyperæmia or excess of free fluid, and distinct from cerebral œdema. Spatz (1929) and others have differentiated two distinct types of swelling of the brain in relation to cerebral tumours: "Hirnschwellung," with an increase in size of the brain substance, which is not due to increase in free fluid, and with a firmer consistency and a dry condition of the tissue, and "Hirnödem," in which the tissue is softer and wetter than normal. In this study, however, no evidence was forthcoming to support any such distinction between brain swelling and œdema.

Summary.

(1) Eighty-three specimens of cerebral tissue were analysed and their water, Na, Cl, K and P contents determined. Various parts of both normal and pathological brain were examined.

(2) Cortical grey matter contains considerably more water (average 84·3 per cent.) than the white matter of the cerebral (70·7 per cent.) and cerebellar (70·6 per cent.) hemispheres, while intermediate values are found for thalamus (75·1 per cent.) and corpus callosum (75·7 per cent.).

(3) By considering the interstitial fluid as a colloid-free ultrafiltrate of serum containing all the chlorides, the composition of the tissue cells themselves is calculated and contrasted with muscle and red cells, the only other tissues for which reliable figures are available. Grey matter has more extracellular tissue (33·0 per cent.) than white matter (18·3 per cent.) and its cellular tissue contains more water (76·5 and 64·1 per cent. respectively). White matter closely resembles both muscle, which has 15·5 per cent. extracellular tissue and the cellular tissue of which contains 67·8 per cent. water, and red cells which contain 66·2 per cent. water.

(4) In the cells of white and grey matter there are 7·8 and 6·9 milliequivs of Na per 100 grm. of cell water respectively, whereas in red cells there is only a small quantity (2·5 milliequivs %) and in muscle cells a negligible quantity (0·29 milliequivs %). The amount of potassium (11·3 and 11·2 milliequivs % in white and grey matter respectively), is approximately equal to the amount in both blood and muscle cells (11·4 and 12·4

milliequivs % respectively). The phosphorus, being nearly all organic, is related rather to the solid than the fluid content; it is present in very large amounts in brain cells, being about equal in grey and white matter when expressed as a percentage of the dry weight (40·0 and 41·7 milliequivs % respectively). This is over twice the quantity present in muscle cells (17·7 milliequivs %) and eight times the quantity in red cells (5·0 per cent.).

(5) Seven cases of local cerebral œdema, six of which were associated with tumour of the brain and one with a recent vascular hæmorrhage, were examined. The differences between water and electrolytic contents of the œdematous tissue and corresponding tissue from the opposite hemisphere were determined in each case. There is a large increase in the fluid content of œdematous brain tissue and this change is restricted to the white matter of the centrum ovale and does not affect the cortex, the thalamus, corpus callosum or internal capsule.

(6) The increase in water, Na, Cl and K in the œdematous tissue are in the same relative proportions as would be the case if the added fluid were a serum filtrate, suggesting that in cerebral œdema, as in œdema of other tissues, there is an increase in the interstitial fluid, derived from the circulating blood. A considerable quantity of additional œdema fluid was found in all cases examined. On the normal side 100 grm. of cellular tissue were associated with an average of 110 grm. extracellular fluid and on the œdematous side with 249 grm. representing an addition of 139 grm. of œdema fluid.

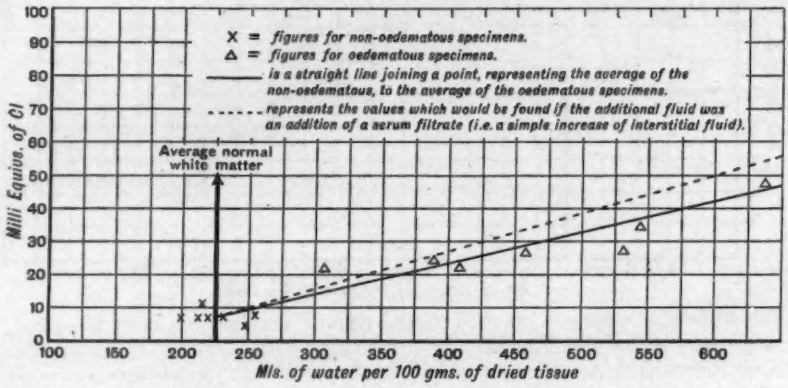
(7) The phosphorus content is slightly but consistently lower on the œdematous side. This may be related to the breakdown of the complex organic compounds in the cellular tissue, associated with the degenerative processes which are seen histologically. This change is probably too small to be of significance.

(8) Identical changes were found in the œdematous tissue related to the recent cerebral hæmorrhage as in the cases of tumour, showing that the changes in cerebral œdema from both these conditions are the same.

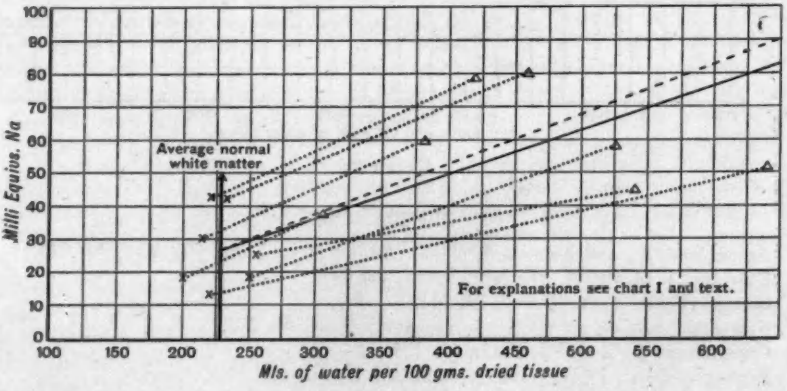
(9) In this study there was no evidence to support the concept that in association with cerebral tumours there also occurs a condition of swelling of the brain ("Hirnschwellung") which is not due to hyperæmia or excess of free fluid, and which can be differentiated from cerebral œdema.

I wish to express my indebtedness to Dr. Greenfield for his encouragement in this work, and for his valuable suggestions and advice; to Dr. Cumings for the generous facilities and help he afforded me; and to Mr. Nunn, B.Sc., for valuable technical help. The work was carried out under a grant from the National Hospital Research Fund (Rockefeller Trust).

GRAPHS I TO IV.


X = figures for non-oedematous specimens.
Δ = figures for oedematous specimens.
——— is a straight line joining a point, representing the average of the non-oedematous, to the average of the oedematous specimens.
------ represents the values which would be found if the additional fluid was an addition of a serum filtrate (i.e. a simple increase of interstitial fluid).
Average normal white matter
Milli Equivs. of Cl
Mls. of water per 100 gms. of dried tissue

GRAPH I.



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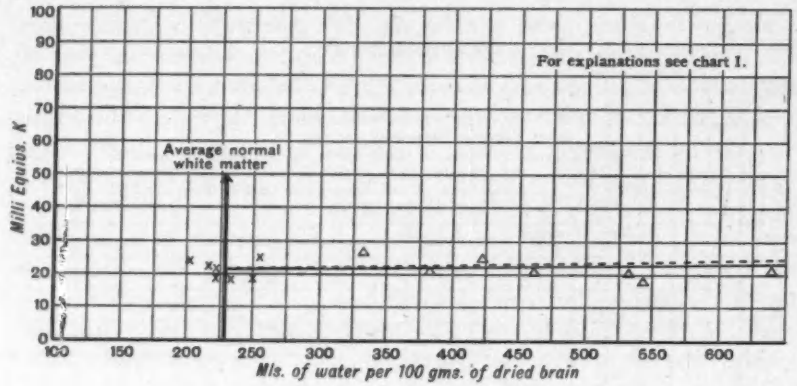

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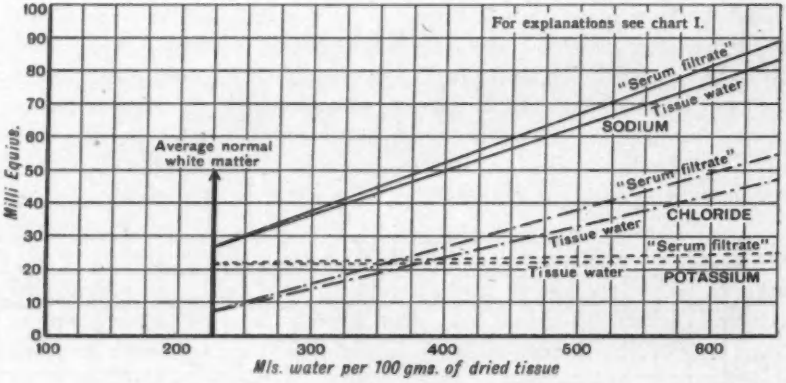

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REFERENCES.

ALEXANDER, L., and LOONEY, J. (1938), *Archiv Neurol. and Psychiat.*, **40**, 877.
CUMINGS, J. N. (1939), *Biochem. Journ.*, **33**, 642.
GERSH, (1938), *Anat. Record*, **70**, 311.
FISKE and SUBBARROW (1925), *Journ. Biol. Chem.*, **66**, 375.
GREENFIELD, J. G. (1939), *Brain*, **62**, 129.
PETERS (1935), "Body Water." Baillière, Tindall and Cox, London.
MCCANCE, R., and SCHIPP, H. (1933), "Chemistry of Flesh Foods." *Spec. Rep. Ser. M. R. C.* No. 187.
SCHLUTER, A., and NEVER, H. (1932), *Ztschr. f. d. Ges. Neur. u. Psychiat.*, **140**, 172.
SPATZ, H. (1929), *Arch. Psychiat. Nervenkr.*, **88**, 790.
WOELFEL, W. (1938), *Journ. Biol. Chem.*, **125**, 219.

Notices of Recent Publications.

Selected Writings of Sir Charles Sherrington. A Testimonial presented by the Neurologists forming the Guarantors of the Journal *Brain*. Compiled and edited by D. Denny-Brown. Hamish Hamilton Medical Books, London. 1939. Pp. 530, 85 figs. Price 25s.

In 1931 the Guarantors of *Brain* published, under the editorship of Dr. James Taylor, two volumes of the "Selected Writings of Dr. Hughlings Jackson." Convinced of the importance to neurological thought of Jackson's philosophical contributions to neurology and impressed by the inaccessibility of his papers, they thought that no better use could be made of the modest resources at their disposal than to place this pioneer work within the reach of neurologists, physiologists and psychologists.

In pursuance of that policy and also out of a deeply felt sense of the obligation under which clinical neurologists and experimental physiologists both lay to Sir Charles Sherrington for his incomparable contributions to the field of knowledge in which both, in their different fashions, labour, the Guarantors felt that a volume of the "Selected Writings of Sir Charles Sherrington" could also usefully be published.

These considerations were of themselves ample justification for the present volume which the Guarantors regard it as a privilege to sponsor. Yet there was still another motive which animated them. There can be few amongst the neurologists or physiologists of our time who have not experienced at the hands of Sir Charles Sherrington the most generous assistance and encouragement and who have not found in his writings a vital source of inspiration to them in their work. He has thus won from them a warmth of personal affection it is given to but few men to command. This volume, then, is the expression of this affection and appreciation.

For many their first introduction to "The Integrative Action of the Nervous System" is an event to be recalled with gratitude. Even at that time, in 1906, the harvest of Sir Charles Sherrington's work was no mean one, but from this rich source fresh work has never ceased to flow, and the time is ripe for a fresh garnering of it.

The Guarantors have been fortunate in securing as their editor for this purpose one who has himself been a distinguished collaborator in the researches it records, and Dr. Denny-Brown, for whom the task has been a labour of love, may be congratulated upon his achievement.

From the wealth of material at his disposal he has made a continuous record which will expose to many for the first time the truly monumental character of Sir Charles Sherrington's life work, and will reveal clearly the logical and unendingly pursued line of thought that has animated and directed it.

The necessary processes of selection and arrangement could have been made only by one deeply familiar with the work, and Dr. Denny-Brown has produced

not a mere compilation but a carefully chosen and edited selection of papers and of parts of papers designed to reveal the development of Sir Charles Sherrington's researches. The book begins with the early work on the distribution of motor and sensory nerve roots and on the afferent nerve supply of muscles, anatomical observations based upon the experimental methods which provided the essential basis for all that was to come after. There follow chapters on the spinal animal, on reciprocal and double reciprocal innervation, on postural reflexes and on the motor area of the cortex. Finally, the deeper analysis of the processes of excitation and of inhibition are described.

A complete bibliography of all Sir Charles Sherrington's writings follows.

Every student of neurology, clinical and experimental, will wish to steep himself in this record of over half a century's labours until his thought is penetrated by its method and outlook. From it he will learn those lessons of logical thought, accurate observation and scientific imagination that have distinguished the work of Sir Charles Sherrington, and have made it a unique monument to the genius of this most modest and generous of men.

In expressing their thanks to Dr. Denny-Brown, the Guarantors would wish to add their expression of appreciation for the care lavished on the production of the volume by the publishers, Messrs. Hamish Hamilton, who have given its readers a volume worthy alike of its author and its theme.

Untoward Effects of Nitrous Oxide Anæsthesia, with particular reference to residual neurologic and psychiatric manifestations. By. C. B. Courville, with a foreword by Yandell Henderson. Pacific Press Publishing Association, California, 1939. Pp. 174, figs. 54. Price 4 dollars 75 cents.

In a monograph which is fully documented, both clinically and pathologically, the author shows that nitrous oxide anæsthesia—except for brief operations—is not free from danger, that for long operations the anæsthesia it induces is accompanied by a measure of anoxæmia that may have serious, when not fatal, consequences.

It is the accompanying anoxic anoxæmia that is the primary source of danger, and it appears that this element is never wholly absent from prolonged nitrous oxide-oxygen anæsthesia.

Clinically, serious and fatal complications fall into four groups: (1) Sudden death under the anæsthesia ; (2) death some hours after the anæsthesia ; (3) survival with permanent symptoms of organic lesion of the brain ; and (4) transient mental and emotional disorders after the anæsthesia.

A series of cases with complete clinical and pathological details exemplify these four categories.

In the first group, death may be partly ascribed to the patient's general state of health at the time of anæsthesia or to the presence of pre-existent morbid lesions, but cases have been observed in which these factors were not demonstrably present and where anoxæmia must be regarded as the sole operative factor. In such cases, pathological examination of the brain reveals no abnormality other than congestion.

In the second group, death may take place after an interval varying from a few hours to a period of weeks or even months. Death in these cases is usually precipitated by respiratory or cardiovascular failure due to an anoxæmia which produced

a progressive disseminated necrosis of the cerebral grey matter. In the short survivals the subject may not regain consciousness after anæsthesia and may have convulsive seizures. In the longer survivals some measure of recovery of consciousness may ensue, but the final stage is one of deepening coma and hyperthermia.

In the third group, the patient survives with symptoms indicative of structural damage to the basal ganglia: e.g. athetosic or choreiform movements, and may show convulsive seizures, and various forms of muscular twitching, muscular rigidity and inco-ordination. In addition progressive dementia and psychotic symptoms have also been observed.

In the fourth group, transient symptoms, such as delayed recovery of consciousness, accesses of crying, disturbances of speech, and muscular twitching may be observed, complete recovery ensuing in a few hours or days.

The author provides conclusive evidence of the primary and essential role played by the anoxic variety of anoxæmia in the production of these complications. Thus, the brain lesions are identical with those produced by the experimental deprivation of oxygen. The cerebral cortex is not uniformly involved, and the lesions consist of (i) a scattered sclerosis of pyramidal cells, (ii) patchy necrosis, (iii) degeneration of one or more cortical layers, (iv) almost total necrosis of numerous small cortical foci. The pia-arachnoid may present an active cellular proliferation. The astrocytes in the affected cortical foci undergo degenerative changes, while those at the periphery of the focus proliferate with the blood-vessels to form a typical astrovascular scar. There is a microglial reaction with the production of compound granular cells, and the oligodendroglia cells show swelling and proliferation. The cortical nerve cells show lipoidal degeneration. The lenticular nucleus is as severely involved as the cortex, sometimes more severely, while the Purkinje cells of the cerebellar cortex are diffusely affected. Nerve cells in the brain-stem appear immune.

Less severe changes of the above kind are found in cases with long survival periods.

In conclusion, the author maintains that nitrous oxide is not entirely the innocuous agent it has been supposed to be, and that there is an inherent danger in the use of this anæsthetic that must constantly be reckoned with, even though the complications described are relatively rare.

The monograph is admirably illustrated by photomicrographs of the lesions described, and constitutes a neuropathological and clinical study of importance.

Die Übertragbare Kinderlähmung mit besonderer Berücksichtigung der Erfahrungen aus der Kölner Epidemie, 1938. Herausgegeben von H. Kleinschmidt. S. Hirzel, Leipzig, 1939. Pp. 339.

This monograph is the work of ten contributors under the editorship of Professor Kleinschmidt, who adds a summary. It records exhaustively the epidemiological, clinical and pathological observations made on the Cologne epidemic of poliomyelitis in 1938. In all some 550 cases were observed.

In addition there are extensive résumés of modern clinical and pathological work on poliomyelitis. In these chapters the different collaborators are not always in harmony in the views expressed. Thus while the chapter on experimental pathology, which nowhere mentions Weston Hurst's pioneer contributions, accepts

the view founded on this work that poliomyelitis is primarily and essentially a virus infection of the central nervous system, not merely an invasion of this system secondary to a general infection, yet the chapter on the preparalytic stage of the malady speaks of this as a general infection. Heinlein, recording the post-mortem findings notes that he observed no changes outside the nervous system specific for poliomyelitis, while Camerer and Joppich who performed lumbar puncture on a large number of contacts report that no less than one-third of these, although in normal health and symptom-free, showed in the cerebrospinal fluid changes typical of poliomyelitis. For such cases they diagnose a "liquor poliomyelitis," surely a state of affairs not compatible with the old and now abandoned notion of a preliminary stage of general infection.

Perhaps the most interesting new observation is that concerning the blood grouping of the observed cases. Children of Groups O and A2 and those showing blood factor N formed the majority of paralysed cases, while those of Groups B and A1 and those with blood factor M largely escaped paralysis. Should this observation be confirmed it will be one of the first indications that blood groups have a clinical importance apart from problems of transfusion.

Finally, the authors agree that the use of convalescent serum after the appearance of clinical symptoms is valueless.

As their criterion for a certain diagnosis of poliomyelitis they take the appropriate changes in the cerebrospinal fluid. Unless this be the standard, no accurate assessment of case incidence is possible, since all local febrile illness in children is apt to be regarded as an abortive poliomyelitis.

The Anatomy of the Nervous System from the Standpoint of Development and Function. By S. W. Ranson. W. B. Saunders Company, Philadelphia, 1939, sixth edition. Pp. 488, figs. 382.

The warm welcome extended to the fifth edition of this excellent textbook may be given with equal confidence to the new and revised sixth edition. The admirable selection of material and its clear presentation make it wholly suitable to the needs of the clinical neurologist as well as to the student of anatomy.

Among the new sections are to be found a summary of recent views on the cortical fields and their functional properties, and on the anatomy and connections of the thalamic nuclei.

In respect of the former, the criticism may perhaps be hazarded that the state of physiological knowledge of the different cortical fields that lie anterior to the fissure of Rolando is not quite so final as the author's statements suggest.

Thus he remarks that "considerable confusion exists as to the use of the term 'motor cortex' . . . " If this be so, it may not be out of place to emphasize that the term is essentially a physiological and not an anatomical one, and that since the appearance of Leyton and Sherrington's classic paper in 1917 it had but one generally accepted and wholly unequivocal meaning for physiologists. In 1934 a new and anatomical sense was given to the term by Fulton who used it as meaning Brodmann's area 4 (Economo's area giganto-pyramidalis FAγ), a meaning it had never previously been given. Such confusion as may now obtain derives from this new morphological rendering of a physiological term. Whether it will prove more useful than its predecessor remains for further research to decide.

Studies on the Morphogenesis of the Brain in Reptiles. By KNUD KRABBE. Einar Munksgaard, Copenhagen, 1939. Pp. 78 with 23 plates. Price 20 kronen.

A minute anatomical study of the development of the brain in a series of reptiles, lavishly illustrated by figures and photomicrographs. An important contribution to the comparative embryology and anatomy of the brain.

Injuries of the Nervous System Including Poisonings. By O. MARBURG and M. HELFAND. New York: Veritas Press. 1939. Pp. 213. Price 3 dollars.

This will prove a disappointing book to the neurological reader, not only on account of the very considerable difficulties the authors have experienced in writing in what for them is a foreign language, but because of the generally unsatisfactory character of the clinical descriptions given. Thus it is stated that lead encephalopathy "cannot be distinguished from any other multilocular lesion of the brain and spinal cord," the description of the ordinary lead palsy describes it bluntly as a paralysis of the extensor muscles, without any mention of the selective incidence of the paralysis within this group. It also speaks vaguely of sensory symptoms in lead palsy and adds that in other respects "the signs and symptoms do not differ from any other form of neuritis."

In a general discussion of the rôle of trauma in provoking organic nervous disease, the authors insist that the trauma must be "adequate," a statement that entirely begs the question. In respect of paralysis agitans it is said that "in cases with a determined predisposition it is quite possible for this disease to be caused by trauma." What is to be understood by such a predisposition we are not told.

Works on injuries of the nervous system are more likely than other neurological writings to find their way into the hands of readers not specially experienced in this branch of medicine, and it is therefore the more unfortunate that the authors have not afforded more reliable guidance to a circle of readers not very well fitted to assess the value of their statements.

A Family with Pick's Disease. By SANDERS, SCHENK and VAN VEEN. Amsterdam: Noord-Hollandsche Uitgeversmaatschappij. 1939. Pp. 123. 26 figs. Price 4 Guilders.

An exhaustive psychological, clinical and pathological study of a family with Pick's disease, with a general consideration of the heredity of the disease. They find that the essential element in the syndrome is an impoverishment of all intentional and conscious acts, which may make its first appearance with aphasic symptoms. Words lose their referential value and cease to stand for anything: the symbol becomes detached from its referent. Later, repetitive movements become prominent and anomalies of social behaviour arise from the developing defect in thought and speech.

Anatomically the lobar atrophy which is the characteristic finding is associated with atrophy of the neurofibrils, most marked in, but not confined to, the cerebral cortex. Changes were also found in the cerebellum, olives, substantia nigra, corpus striatum, thalamus and diencephalon.

The placing of Pick's disease in relation to the heredo-degenerations, and other attempts to classify it appear to the authors not yet possible.

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